

Gene therapy with etranacogene dezaparvovec in haemophilia B: about the 1st patient infused in Spain

Terapia génica con etranacogene dezaparvovec en hemofilia B: a propósito del primer paciente infundido en España

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Abstract

Introduction: Etranacogene dezaparvovec (ED) is the first gene therapy approved in Europe for severe or moderately severe haemophilia B without inhibitors. Its implementation in Spain began in 2024 as an alternative to conventional FIX prophylaxis.

Objective: To describe the initial clinical experience and 3-month outcomes of the first patient treated with ED in Spain, in the context of the 5-year HOPE-B data. **Materials and methods:** Data collection from the patient's electronic medical record.

Results: A 41-year-old male with baseline FIX 1.6% and advanced arthropathy received a single intravenous dose of ED. Infusion was well tolerated, with immediate discontinuation of prophylaxis. FIX activity increased progressively to 49.9% at 3 months, placing the patient at the 67th percentile of the HOPE-B trial (mean 39.0 IU/dl at month 6; 36.1 ± 15.7 IU/dl at 5 years). Mild and transient transaminitis was managed with prednisone without additional complications. **Conclusions:** Initial results confirm the expected safety and efficacy of ED in real clinical practice, consistent with the long-term HOPE-B profile, and highlight the importance of careful patient selection and motivation.

Keywords: Haemophilia B. Gene therapy. Etranacogene dezaparvovec. Factor IX coagulative activity.

Resumen

Introducción: Etranacogene dezaparvovec (ED) es la primera terapia génica aprobada en Europa para hemofilia B grave o moderadamente grave sin inhibidores. Su implementación en España comenzó en 2024 como alternativa a la profilaxis convencional con factor IX (FIX). **Objetivo:** Describir la experiencia clínica inicial y los resultados a tres meses del primer paciente tratado con ED en España, en el contexto de los datos de 5 años del ensayo HOPE-B. **Material y métodos:** Recogida de datos de la historia clínica electrónica del paciente. **Resultados:** Varón de 41 años, FIX basal 1,6% y artropatía avanzada, recibió una dosis única intravenosa de ED. La infusión fue bien tolerada con suspensión inmediata de la profilaxis. La actividad de FIX aumentó progresivamente hasta el 49,9% a los tres meses, situando al paciente en el percentil 67 del ensayo HOPE-B (media 39,0 UI/dl al mes 6; $36,1 \pm 15,7$ UI/dl a los 5 años). Se observó transaminitis leve y transitoria, controlada con prednisona, sin complicaciones adicionales. **Conclusiones:** Los resultados iniciales confirman la seguridad y eficacia esperadas de ED en práctica clínica real, consistentes con el perfil a largo plazo del HOPE-B, y subrayan la importancia de una selección cuidadosa y la motivación del paciente.

Palabras clave: Hemofilia B. Terapia génica. Etranacogene dezaparvovec. Factor IX coagulativo.

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Introduction

Etranacogene dezaparvovec (ED) is the first gene therapy approved by the European Medicines Agency (EMA) in 2023 for adult patients with severe or moderately severe haemophilia B (HB) (factor IX [FIX] $\leq 2\%$) without inhibitors, based on the results of the HOPE-B clinical trial.¹ In Spain, it has been available since September 2024 following approval by the Interministerial Commission on Medicine Prices.² At present, there is no national reference network for infusion centres, as proposed by the EAHAD (European Association of Haemophilia and Allied Disorders) and the UKCHDO (United Kingdom Haemophilia Centre Doctors' Organisation),^{3,4} which advocate the implementation of a hub-and-spoke model with clearly defined functions.

ED is expected to provide long-term functional correction of HB by enabling endogenous FIX production after a single intravenous administration. Data from the final 5-year HOPE-B analysis.⁵ (published in December 2025 in the *New England Journal of Medicine*) confirm that a single dose of ED induced durable and effective FIX Padua expression for 5 years in patients with severe or moderately severe HB. In the full analysis population ($n = 54$), the overall annualised bleeding rate (ABR) was 4.16 during the lead-in period and 1.52 during months 7–60 after gene therapy, representing a 63% reduction (95%CI, 24–82). Mean endogenous FIX activity remained stable throughout the 5-year follow-up, with a value of 36.1 ± 15.7 IU/dl at year 5; 80% of participants had FIX activity ≥ 12 IU/dl at that time (Fig. 1). Exogenous FIX consumption was reduced by 96%, from 257,339 IU/year during the lead-in period to 10,924 IU/year during months 7–60. A total of 94% of participants (51/54) discontinued continuous FIX prophylaxis without restarting it during the 5-year follow-up. No FIX inhibitors or thrombotic events were detected during the analysis period.

Despite the high cost of treatment, the adoption of outcome-based payment models appears to be a reasonable strategy, as it makes the initial economic impact on public health systems more flexible. Durability of FIX expression for up to 20–25 years has been estimated for $> 80\%$ of recipients, according to Bayesian models,⁶ which require confirmation with prospective longitudinal data. This estimate is consistent with the results of the AMT-060 study,⁷ the precursor platform of ED, which uses the wild-type FIX transgene instead of the Padua variant, with stable FIX levels at 8 years – although around 5%, lower than those achieved with

ED – confirming the long-term feasibility and safety of the AAV5 platform.

Method

We describe the initial clinical experience and 3-month outcomes of the first patient treated with ED in Spain. Clinical data were obtained from the electronic medical record and laboratory reports. The study was approved by the centre's Research Ethics Committee, and written informed consent was obtained.

Results

The patient was a 41-year-old man with moderately severe HB (baseline FIX 1.6%; genotype c.892C>T, exon 8, F9 gene, pathogenic variant generating a stop codon) receiving secondary prophylaxis with eftrenonacog alfa (50 IU/kg weekly) since 2018, with no current or previous history of FIX inhibitors. The patient had advanced haemophilic arthropathy (HEAD-US score: 7), predominantly affecting the ankles and left elbow. Baseline characteristics are shown in [table 1](#).

Before requesting authorisation for infusion, compliance with all inclusion criteria and none of the exclusion criteria was certified, in accordance with the Therapeutic Positioning Report of the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS).⁸ The patient had a past medical history of resolved hepatitis C virus (HCV) infection, with liver stiffness by FibroScan of 3.1 kPa and normal abdominal ultrasound. Anti-AAV5 antibody titres were < 18.5 (lower limit of detection, AAV5 NAb Test Precision for Medicine®) in 2 determinations performed 2 months apart. Serology for the remaining hepatotropic viruses and HIV tested negative. Baseline liver biochemistry parameters and creatine phosphokinase (CPK) were normal.

Before signing the informed consent form, after delivery of the Gene Therapy Questions and Answers Guide for patients⁹ and following the roadmap described by Álvarez-Román et al.,¹⁰ the patient was evaluated by the clinical psychologist, who certified that he understood the process and his obligations. The informed consent form was prepared jointly by the Departments of Haematology and Pharmacy, with special emphasis on postinfusion obligations, including prohibition of alcohol consumption and use of barrier methods within the first year.

On 18 June 2025, the patient was admitted to the haematology unit. After confirming the absence of contraindications, ED was administered at a dose of

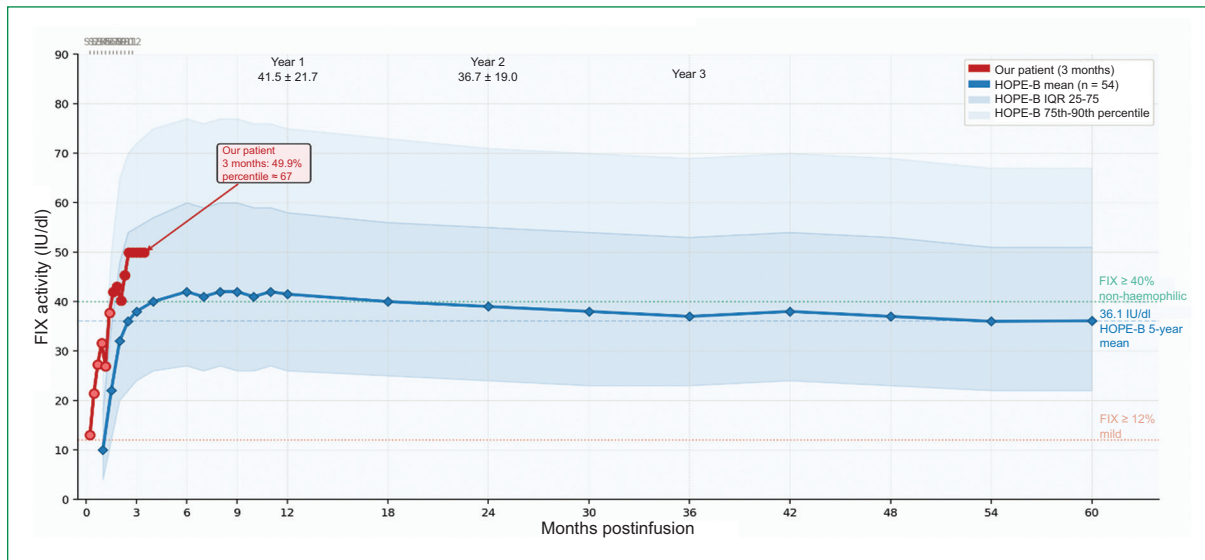


Figure 1. Endogenous FIX levels: our patient vs the HOPE-B trial (5-year follow-up) (*adapted from Pipe et al.⁹*). Comparison of endogenous FIX activity (IU/dL) between our patient (red line, circles) and participants in the HOPE-B trial (n = 54) within the 5-year follow-up. Blue line: HOPE-B arithmetic mean. Dark blue band: IQR (P25-P75). Light blue band: 75th–90th percentile. Reference lines: FIX ≥ 40 IU/dL (green dotted line, non-haemophilic threshold), FIX ≥ 12 IU/dL (orange dotted line, mild haemophilia threshold), HOPE-B mean at year 5: 36.1 IU/dL (blue dashed line). The upper axis shows the correspondence in weeks within the first 3 months. The annotation indicates the position of our patient at week 15 (FIX 49.9%, percentile ≈ 67). FIX: factor IX.

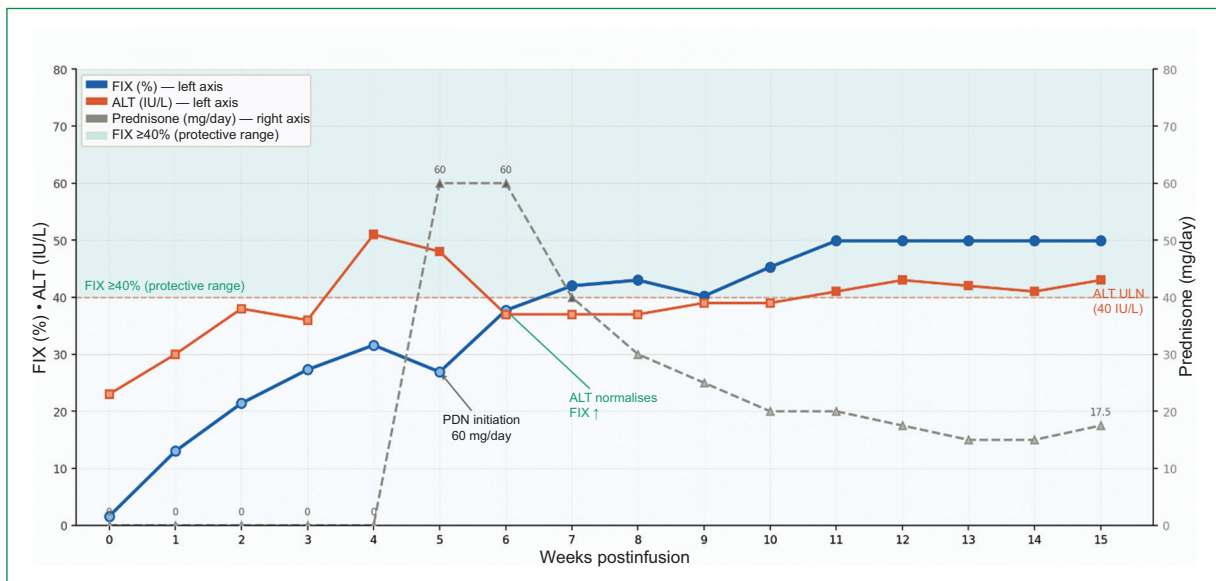


Figure 2. Evolution of FIX activity, ALT, and PDN dose (weeks 0–15 postinfusion). Weekly evolution of FIX activity (%) (blue line, circles; left axis), ALT (IU/L) (orange line, squares; left axis), and PDN dose (mg/day) (grey dashed line, triangles; right axis) during the first 15 weeks postinfusion of etranacogene dezaparvovec. The shaded green area indicates the FIX ≥ 40% range (protective range). The orange dashed line indicates the ALT ULN (40 IU/L). Dark blue FIX points: ≥ 40%. Light blue FIX points: < 40%. ALT: alanine transaminase; FIX: factor IX; PDN: prednisone; ULN: upper limit of normal.

Table 1. Patient baseline characteristics

Parameter	Value
Age	41 years
Sex	Male
Diagnosis	Moderately severe haemophilia B
Baseline FIX activity	1.6% (one-stage clotting assay)
F9 genotype	c. 892C > T, exon 8 – stop codon (moderately severe/severe phenotype)
Previous prophylaxis	Eftrenonacog alfa 50 IU/kg/week since 2018
Anti-FIX inhibitors	Negative (no history)
Haemophilic arthropathy	Advanced (HEAD-US: 7); ankles and left elbow
Previous HCV infection	Resolved. FibroScan: 3.1 kPa. Normal abdominal ultrasound
Hepatotropic virus and HIV serology	Negative
Anti-AAV5 antibodies	< 18.5 (negative; AAV5 NAb Test Precision for Medicine®; 2 determinations)
Baseline liver function	Normal ALT, AST, GGT, and bilirubin levels
Baseline CPK	Normal
Psychological evaluation	Suitable; understands postinfusion risks and obligations
Informed consent	Signed after multidisciplinary evaluation
Infusion date	18 June 2025
Dose administered	2×10^{13} gc/kg intravenously

AAV5: adeno-associated virus type 5; ALT: alanine transaminase; AST: aspartate transaminase; CPK: creatine phosphokinase; FIX: factor IX; gc: genome copies; GGT: gamma-glutamyl transferase; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

2×10^{13} gc/kg intravenously over 1 h. The infusion was well tolerated, with no adverse events. EHL-FIX prophylaxis was discontinued on the same day. The patient remained under observation and was discharged 4 h later, with weekly follow-up visits initiated according to the centre's protocol, based on international recommendations and the product's summary of product characteristics.

Within the first days after administration, the patient reported greater tiredness than usual, remained afebrile, and experienced transient headache and myalgia within the first 24 h. These symptoms did not prevent him from carrying out his work activity and did not

require specific management. From week 1 to week 4, FIX activity progressively increased from 13 to 31.6% (one-stage clotting assay, HemosIL SynthASil®, ACLTop®), while alanine transaminase (ALT) levels remained within the normal range.

At week 4, ALT increased to 51 IU/L (upper limit of normal [ULN]: 40 IU/L; last baseline value: 30 IU/L on 6 June 2025), with normal aspartate aminotransferase (AST), total bilirubin, and CPK. Forty-eight hours later, ALT spontaneously decreased to 41 IU/L, with a slight decrease in FIX to 28.3% – below the critical threshold of 20–30%. Four days later, ALT increased again to 48 IU/L and FIX decreased to 26.9%, a 15% decrease from peak, with all other parameters remaining normal. In accordance with our protocol and the HOPE-B data, interpreting the sustained increase in ALT as an immune response against the gene vector, prednisone 60 mg/day was started. After 7 days (week 6 postinfusion), ALT normalised and FIX increased to 37.7%.

Thereafter, prednisone was progressively reduced to 40 mg/day, with weekly clinical and laboratory follow-up. At week 15, FIX was 49.9%, ALT was 43 IU/L, and the prednisone regimen was 20–15 mg on alternate days. No bleeding episodes have occurred and no FIX concentrate administration has been required up to the closing date of this report (Fig. 2). Laboratory determinations are always performed using the same equipment to minimise variability in longitudinal follow-up.

Conclusions

We report the first 3 months of follow-up after the first ED infusion performed in Spain. Although the follow-up period is still short, treatment evolution has been successful to date. The patient reports a high degree of satisfaction, despite the demanding follow-up programme with weekly visits during the first months, which will continue until corticosteroid therapy is discontinued. The patient's strong motivation for gene therapy is a factor that we consider essential in candidate selection. Unlike the roadmap described by Álvarez-Román et al.,¹⁰ in our case, a hepatologist was not included in the multidisciplinary team because the previous liver assessment was normal.

Infusion tolerance was excellent, in line with the HOPE-B safety profile, in which only 1 patient (1.9%) discontinued the infusion because of an infusion reaction, receiving only 10% of the planned dose.⁵ Postinfusion symptoms – fatigue, headache, and myalgia during the first 24 h – correspond to those listed as very common ($\geq 10\%$) in the summary of product

characteristics, are self-limiting, and do not require additional measures. The 3-month course follows the expected pattern: good infusion tolerance, mild and reversible elevation of liver enzymes, and satisfactory FIX levels. In HOPE-B, detectable FIX activity appears during the first week postinfusion, with a progressive increase and a stable plateau around weeks 6–8. Mean endogenous FIX was 41.5 ± 21.7 IU/dL (median: 39.9; range: 5.9–113) at year 1, 36.7 ± 19.0 IU/dL at 2 years,¹¹ and 36.1 ± 15.7 IU/dL at year 5,⁵ showing remarkable stability over time (Fig. 1). Our patient's levels (49.9% at week 15) are consistent both in the dynamics of increase and in magnitude, placing him at approximately the 67th percentile of the pivotal trial. The final 5-year HOPE-B analysis further confirms that 96% of responding participants (51/52) maintained durable protection against bleeding during months 7–60 without restarting prophylaxis.

Regarding laboratory monitoring, the one-stage clotting assay is the recommended method in clinical practice for follow-up of patients with HB after gene therapy with FIX Padua.¹² Astermark et al.¹² emphasise that this method is appropriate and reliable – unlike the chromogenic assay, which tends to underestimate FIX activity – and that the same reagent should always be maintained to reduce longitudinal variability. At our centre, we use HemosIL SynthASil®, for which the authors report better agreement between central and local laboratories.

The observed transaminitis is consistent with a specific hepatocyte-mediated immune response against the AAV5 vector or the expressed transgene, without multiorgan or muscular damage, as reflected by normal AST, CPK, and bilirubin levels. In the 5-year HOPE-B analysis,⁵ early ALT elevations – defined as an increase $\geq 2 \times$ baseline level or $>$ ULN within the first 4 months – were observed in 11 participants (20.4%), of whom 9 (16.7%) received systemic glucocorticoids for a mean of 81.4 ± 28.6 days (range 51–130). The incidence of these elevations was lower than that observed in previous trials of liver-directed gene therapy with AAV vectors. Importantly, participants with early ALT elevation had slightly lower mean FIX levels in the long term – although still within the therapeutic range – than those who did not develop it. Corticosteroid management in our patient is within the expected range and was not associated with worse prognosis in the pivotal trial. The French series¹³ reported transient ALT elevations in 2 of 3 infused patients, without the need for corticosteroids. Immunosuppression in our patient is

being adapted according to clinical and laboratory evolution.

From the standpoint of long-term safety, the final 5-year HOPE-B analysis⁵ detected no evidence of treatment-related oncogenicity, late liver dysfunction, or thromboembolic events. The hepatocellular carcinoma diagnosed in 1 participant was determined not to be related to ED after independent molecular analysis of vector integration. This safety profile is particularly relevant given that more than half of HOPE-B participants had positive serology for HCV or hepatitis B virus (HBV) at screening, a situation also present in our patient, who had resolved HCV infection.

In parallel, a group of Spanish haematologists has begun developing an artificial intelligence platform aimed at selecting and monitoring patients who are candidates for gene therapy for HB (<https://codigorojo.tech/home/>), in line with the findings reported by Succi et al.¹⁴ on the potential of AI for clinical training in rare diseases. To date, the system's recommendations are concordant with those of the clinicians involved.

In conclusion, ED administration in the first Spanish patient has proven safe and effective at 3 months of follow-up, with FIX expression in the therapeutic range, absence of bleeding, and successful management of transaminitis with corticosteroids. These results are fully consistent with the pattern of efficacy and safety confirmed by the final 5-year HOPE-B analysis. Selection of motivated and well-informed patients may be a determining factor for the success of this treatment. Long-term follow-up will make it possible to confirm the durability of response.

Funding

None declared.

Conflicts of interest

None declared.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymised clinical data. Following to the nature of the study, individual informed consent was not

required. The relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that OpenAI was used for figure 1.

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