

Etranacogene Dezaparvovec: 15-Month Follow-Up of the First Patient Infused in Spain

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Review began 10/13/2026

Review ended 10/25/2026

Published 10/28/2026

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DOI: 10.7759/cureus.118715

Abstract

Etranacogene dezaparvovec is an adeno-associated viral vector gene therapy (GT) for severe and moderately severe haemophilia B. In Spain, it is reimbursed under a five-year outcomes-based payment agreement recorded on the public VALTERMED platform (Ministerio de Sanidad, Madrid, Spain). Real-world experience remains limited, and follow-up of liver events that appear late after the infusion is scarcer still. We report the complete 15-month course of the first patient treated commercially with this therapy in Spain. He was a 42-year-old man with moderately severe haemophilia B (baseline factor IX (FIX) activity 1.6 IU/dL), established haemophilic arthropathy, a Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) score of 23, and cured hepatitis C. Neutralising antibodies against adeno-associated virus serotype 5 were undetectable. He had been on prophylaxis with recombinant factor IX linked to Fc at a dose of 60 IU/kg every seven days for six years, with a mean trough of 5.5% and an annualised bleeding rate of 1.66. He received a single intravenous infusion of 2×10^{13} genome copies (gc)/kg in 2025, stopping prophylaxis the following day. Monitoring was weekly during the first months, with FIX, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine phosphokinase (CPK) measured in the same laboratory. FIX activity rose to a plateau of 50–65 IU/dL and stayed there. None of the 65 determinations fell below 5%, and 89% exceeded 40%. The annualised bleeding rate fell from 1.66 to 0, and factor use was limited to 2,000 IU on day +1. The HEAD-US score did not change. There were four ALT elevations. The first two, on day +34 and during the taper, required full-dose prednisone (PDN): corticosteroid treatment lasted 335 days, with about 7.4 g in total. The last two appeared off corticosteroids, 11 days after withdrawal and in month 15. The third resolved with observation alone. The fourth was treated with PDN 15 mg/day for seven days, after which ALT fell to 50 IU/L and FIX rose to 64.8 IU/dL, and the PDN dose was then reduced to 10 mg/day. That episode has since resolved, with ALT 26 IU/L and FIX 58.3 IU/dL at the most recent determination, on day +491. No second-line immunosuppression was given. At 15 months after a single infusion, FIX expression remains in the non-haemophilic range and the patient is clinically well, with no bleeding and no factor use. The first-year milestone of the payment agreement has been verified. The price was prolonged corticosteroid exposure, in a scenario for which we found no published guidance.

Categories: Therapeutics, Hematology

Keywords: corticosteroids, cost-benefit analysis, dependovirus, factor ix, gene therapy, haemophilia b, real-world evidence, transaminases

Introduction

Prophylaxis is the standard of care in severe haemophilia and in much of moderately severe disease [1]. It protects, but it carries a high treatment burden, with lifelong infusions, and the cumulative cost is high [2]. Extended half-life factor IX (FIX) concentrates, such as recombinant FIX Fc fusion protein (rFIXFc), have widened dosing intervals and improved adherence [3]. Even so, some patients keep bleeding with apparently protective troughs. The relationship between FIX activity and the annualised bleeding rate (ABR) is not linear, and protection rises steeply only above the mild haemophilia range [4].

Etranacogene dezaparvovec (ED) is a serotype 5 adeno-associated viral vector (AAV5) carrying the Padua variant of the FIX gene [5]. A single intravenous infusion delivers the vector to the liver, where transduced hepatocytes express the transgene and secrete factor IX. The Padua variant is a naturally occurring gain-of-function change that gives the protein several times the specific activity of wild-type factor IX, so a modest amount of transgene product yields a disproportionate rise in measured activity. The transgene remains episomal rather than integrating into the genome, which means that expression depends on how many transduced hepatocytes survive. That is the reason why anything that destroys those cells threatens the durability of the response. The pivotal HOPE-B trial and its final analysis at five years confirmed a mean activity of 36.1 ± 15.7 IU/dL, a 63% reduction in ABR and a favourable safety profile [6,7]. Two activity thresholds recur in what follows. Activity above 5% lifts a patient out of the severe range, and it is the level the Spanish agreement uses to define a maintained response. Activity above 40% is the lower limit of the normal range, at which no haemostatic deficit is expected. In Spain, ED has been the first gene therapy (GT) reimbursed for haemophilia B (HB), with a specific patient journey proposed by the BHEMOGEN project [8]. The therapeutic positioning report of the Spanish Agency of Medicines and Medical Devices (AEMPS) positions it as an option for adults with severe or moderately severe HB, with no history of FIX inhibitor and

How to cite this article

Lopez M R, Amoedo Bastos A, Lopez Ansoar E, et al. (October 28, 2026) Etranacogene Dezaparvovec: 15-Month Follow-Up of the First Patient Infused in Spain . Cureus 18(10): e118715. DOI 10.7759/cureus.118715

no high anti-AAV5 antibody titres [9]. Neutralising antibodies against the vector capsid are relevant because they can prevent hepatocyte transduction, which is why titres are measured before treatment. HOPE-B did not exclude participants on that basis, and efficacy did not differ substantially according to the baseline titre [7]. It is subject to a five-year outcomes-based payment agreement recorded on the public VALTERMED platform. That agreement sets the funding conditions, which include at least two years of previous prophylaxis with an extended half-life FIX concentrate, and the annual payments continue while FIX activity stays above 5% without prophylaxis [10].

The main adverse event associated with ED is the rise in transaminases. It is the principal threat to transgene expression, because it is thought to reflect a T-cell response against the viral capsid displayed by transduced hepatocytes, and the destruction of those cells costs expression that cannot be recovered. This is why an ALT rise accompanied by a fall in factor IX activity is treated with corticosteroids, and why the two must be read together rather than separately. In HOPE-B, it occurred in 11 of 54 participants, always as a single episode within the first 12 weeks, and responded to corticosteroid monotherapy over a mean of 81.4 ± 28.6 days [7]. What to do when the pattern repeats, how long to prolong the corticosteroid treatment and when to add a second immunosuppressant are not settled in any protocol. We describe the 15-month course of the first patient treated commercially with ED in Spain. This report covers high-density monitoring of the complete liver course up to corticosteroid withdrawal and beyond, together with haemostatic efficacy, joint health and the verification of the first milestone of the outcomes-based payment agreement. The biphasic pattern of the first two liver episodes and the immunosuppressive decisions taken at that time were reported in preliminary form as a letter to the editor [11]. Preliminary economic and durability results were presented as meeting abstracts at the most recent ISTH Congress (Paris, July 2026).

Case Presentation

Patient and baseline status

The patient was a 42-year-old man weighing 75 kg, with moderately severe HB (baseline endogenous FIX activity 1.6 IU/dL) and no current or previous history of FIX inhibitor. He had recurrent haemarthrosis and chronic elbow arthropathy. Hepatitis B virus and human immunodeficiency virus serologies were negative. He had a history of cured hepatitis C, with positive anti-hepatitis C virus antibodies. Liver elastography showed 3.1 kPa, and abdominal ultrasound was normal, with no steatosis. The anti-AAV5 neutralising antibody titre was below 18.5, under the limit of quantification, in two determinations before the infusion (Precision for Medicine, Frederick, MD). Mean alanine aminotransferase (ALT) over the previous six months was 36.6 IU/L, range 23–53 IU/L, with an upper limit of normal (ULN) of 40 IU/L. Occasional intra-individual fluctuations above the ULN were recorded in the absence of active liver disease.

The patient had been on prophylaxis with rFIXFc (eftrenonacog alfa) 60 IU/kg every seven days since 2018. His mean FIX trough was 5.5%, adherence was above 90% and mean consumption was 234,000 IU/year. Mean ABR over the previous three years was 1.66, that is, five bleeds over three patient-years, mostly spontaneous elbow haemarthrosis. The baseline Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) score, obtained four months before the infusion, was 23 [12].

Selection and infusion

The patient was selected following the BHEMOGEN patient journey [8] and the criteria of the therapeutic positioning report [9]. The Spanish reimbursement agreement requires at least two years of previous prophylaxis with an extended half-life FIX concentrate [10], unlike HOPE-B, which required 150 days of previous exposure or at least six months of prophylaxis [6]. After assessment by the multidisciplinary committee of our centre, authorisation by the health authority and the signing of informed consent, ED was given in June 2025 as a single intravenous dose of 2×10^{13} gc/kg. The infusion took 1 hour and was uneventful. The patient stayed 5 hours under observation and was discharged home the same day. Prophylaxis was stopped after a last dose of 2,000 IU on day +1.

Monitoring and definitions

Monitoring followed the local protocol, based on the summary of product characteristics and on published HOPE-B data [6,13]. FIX activity was measured with a one-stage clotting assay (SynthASil, Werfen, Barcelona, Spain), since the chromogenic method gives lower values [14]. ALT, aspartate aminotransferase (AST), creatine phosphokinase (CPK) and full liver function tests were measured together with FIX, always in the same laboratory and on the same analyser. Testing was weekly during the first three months. It then remained weekly or fortnightly for as long as corticosteroid treatment continued, and was spaced out progressively thereafter. ABR was defined as the number of confirmed bleeding episodes per year, separating spontaneous from traumatic ones [1]. Joint health was assessed with HEAD-US [12]. The immunosuppressive strategy was reactive throughout.

Economic analysis

A cost-offset analysis was performed from the perspective of the Spanish National Health System (SNS), with a 20-year horizon and a 3% annual discount rate. The comparator was the patient's own prophylaxis

before GT, that is, 234,000 IU/year of rFIXFc at €0.73/IU, the public price of the INGESA framework agreement net of the statutory deduction [15], with a cost per bleed of about €2,820. The GT arm reproduced the outcomes-based payment scheme recorded on VALTERMED [10]. This includes an initial payment and payments conditional on response at 12, 24, 36, 48 and 60 months, and the resumption of previous prophylaxis if response is lost. The terms of the agreement are not publicly available, so the distribution of payments used here is a model consistent with the published total and with the verification milestones. Durability is the parameter that governs the result and the one that 15 months of follow-up cannot inform, so it was handled as a one-way sensitivity analysis: the duration of response was varied across predefined scenarios from 5 to 20 years, and the whole range is reported rather than a single central estimate. A second scenario replaced the staggered scheme with a single upfront payment, to test how much the result depends on the modelled split between instalments. Administration and monitoring costs were not estimated, as they are marginal relative to the acquisition cost and directionally ambiguous. No utilities or quality-of-life data were available, so the analysis is a cost offset and not a cost-utility analysis. The full list of assumptions is set out in the legend of Figure 1.

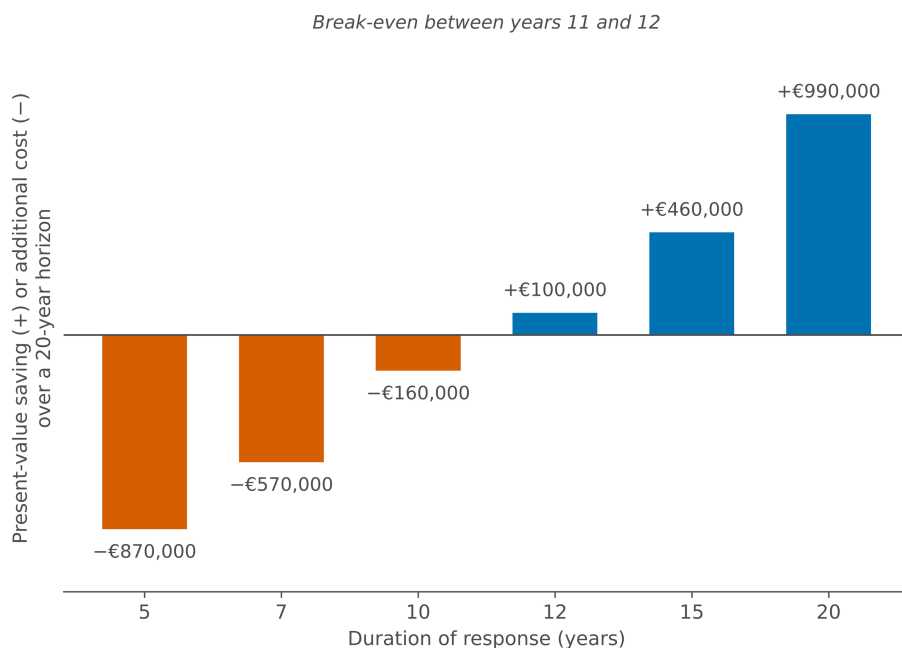


FIGURE 1: Saving or additional cost in present value at 20 years according to the duration of the response.

The comparison is with the patient's own prophylaxis before gene therapy. The assumptions behind the projection are listed in the panel below the chart: perspective, horizon, discount rate, the composition of the comparator, the structure of the payment scheme, and what the model excludes. The duration of response is varied from 5 to 20 years as a one-way sensitivity analysis, and the break-even point lies between years 11 and 12. The bars are projections under each scenario, not savings that have been realised.

Image credit: Manuel R. López.

Factor IX activity kinetics

FIX activity began to rise in the first week and continued to do so progressively. On day +7 the plasma level was 19.1 IU/dL. It reached 31.3 IU/dL on day +27. It fell transiently, coinciding with the first liver episode. After prednisone (PDN) was started it rose again, to 66.7 IU/dL in month 4. From then on it stayed on a plateau between 50 and 65 IU/dL, with fluctuations that were not accompanied by clinical change. None of the 65 determinations performed fell below 5%. A total of 89% exceeded 40%, the lower limit of the non-haemophilic range. The net increase over the previous trough of 5.5% was more than 45 percentage points, above the HOPE-B mean [7]. The course by period is shown in Table 1.

Period	n	Mean FIX ± SD (IU/dL)	Range (IU/dL)	≥5%	≥40%
Weeks 1-4	4	24.8 ± 5.6	19.1-31.3	100%	0%
Weeks 5-8	5	35.6 ± 7.5	26.9-43.0	100%	40%
Weeks 9-16	9	48.8 ± 4.8	40.2-55.0	100%	100%
Weeks 17-24	11	59.6 ± 5.3	50.0-66.7	100%	100%
Months 7-9	15	61.0 ± 8.1	50.0-78.8	100%	100%
Months 10-12	11	56.7 ± 7.0	49.5-72.8	100%	100%
Months 13-15	10	54.3 ± 4.4	48.0-65.0	100%	100%
Total (15 months)	65	53.1 ± 11.7	19.1-78.8	100%	89%

TABLE 1: Factor IX activity by period after the infusion of etranacogene dezaparvovec.

Measured with a one-stage clotting assay. The 5% threshold is the criterion of the reimbursement agreement and 40% is the lower limit of the non-haemophilic range.

FIX, factor IX; SD, standard deviation

Clinical efficacy

There were no bleeding episodes over 15 months. ABR fell from 1.66 to 0. Spontaneous and joint bleeds disappeared. FIX concentrate use after GT was limited to the 2,000 IU dose on day +1, compared with 234,000 IU/year before. He needed no factor for any other reason, and no invasive procedures were performed during follow-up.

Joint health

The HEAD-US score was reassessed at 11.5 months and was still 23. There was no ultrasound progression, although reversal of established chronic arthropathy was not to be expected [12]. A one-year interval is too short to speak of stabilisation. The patient reported that his elbow pain had gone. He also progressively stopped taking analgesics, a finding he reported himself and not one collected with a validated pain instrument.

Liver safety and the course of immunosuppression

There were four ALT elevations during follow-up. The first two called for full-dose corticosteroid treatment. The third was managed with observation alone. The fourth received a short low-dose course.

On day +27, a transient elevation up to 51 IU/L was detected, 1.3×ULN, with no fall in FIX. At 48 hours ALT had come down to 41 IU/L spontaneously, with no treatment. A week later, on day +34, it rose again to 48 IU/L, 1.2×ULN and 1.3× the patient’s own baseline, this time with a concomitant fall in plasma FIX from 51.3 to 26.9 IU/dL, a 14% drop. PDN 60 mg/day was started, following the recommendation of the summary of product characteristics to treat any ALT above the reference limit or above twice the baseline value [13]. ALT normalised in seven days, FIX resumed its rise and a conventional taper of about 10 mg per week was begun.

The second episode appeared on day +105, with PDN already at 15 mg/day. ALT rose to 63 IU/L and, as the elevation persisted after 4 days, the dose was re-escalated to 60 mg/day. The peak was reached on day +112: 74 IU/L, 1.9×ULN and 2.0× baseline. This time there was no fall in FIX, which stayed between 49.3 and 53.3 IU/dL during the days around the peak and exceeded 60 IU/dL from day +121. The differential work-up was negative. It included a liver autoimmunity panel, serologies for hepatotropic viruses with hepatitis B virus DNA polymerase chain reaction to rule out occult infection, immunoglobulins and a repeat abdominal ultrasound. CPK stayed within the reference range throughout follow-up, 31 to 152 IU/L (reference 21-308 IU/L), which ruled out an extrahepatic origin of the enzyme rise. ALT began to fall two weeks after re-escalation. From then on the PDN taper was slower: weekly reductions of 5 mg until April 2026 and then a stable dose of 5 mg/day until it was stopped in June 2026. At no point was a second immunosuppressant added.

Corticosteroid treatment was continuous from day +34 to complete withdrawal on day +369: 335 days and about 7,420 mg of cumulative PDN, compared with a maximum of 130 days in HOPE-B [7]. The patient gained 5 kg. Blood glucose and blood pressure stayed normal at every check. He received prophylaxis with trimethoprim-sulfamethoxazole twice daily on three days a week until the PDN dose fell below 15 mg/day,

together with calcium and vitamin D supplements. Adrenal function was not assessed after withdrawal.

The third elevation occurred on 3 July 2026, on day +380, 11 days after the last dose of PDN, with a maximum of 72 IU/L. It came with a simultaneous rise in FIX up to 65 IU/dL, not a fall. It was not treated. ALT came down to 41 IU/L on day +391 and then fluctuated for another month, with 63 and 62 IU/L on days +398 and +405, always untreated and with FIX between 52 and 55 IU/dL. At the month 14 visit, on day +433, ALT was 42 IU/L and FIX 54 IU/dL, above the mean plus one standard deviation of the HOPE-B cohort. The patient had been nine weeks off corticosteroid, with no bleeding and no factor use since day +1. At that point we suspected possible interference related to the patient’s night shifts.

The fourth peak appeared on day +460, with an ALT of 82 IU/L. FIX fell from 54 to 48 IU/dL, that is 6 percentage points, an 11% relative drop, without leaving the non-haemophilic range. At seven days, ALT had risen to 88 IU/L, 2.2×ULN and 2.4× baseline, and FIX had recovered to 50.8 IU/dL. The rest of the liver profile and CPK stayed normal, which again ruled out an extrahepatic origin and a cholestatic pattern. The patient was asked about dietary changes, alcohol and drug intake, and none were reported. Surveillance became weekly. After consulting hepatology we decided to reintroduce PDN at 15 mg/day for seven days, to rule out a residual immune response. It is worth saying plainly: 88 IU/L exceeds the threshold of the summary of product characteristics, which recommends treating any ALT above the reference limit or above twice the baseline value [13]. We chose a low dose and a short course instead of the 60 mg/day of the first two episodes. That choice has no support in trial data. It rests on the course of the previous episode and on the stability of FIX, and it should be read as an individual clinical decision taken under uncertainty, not as a regimen we are proposing for others. At seven days, on day +474, ALT had come down to 50 IU/L and FIX had risen to 64.8 IU/dL, with the remaining parameters within normal limits. We then reduced PDN to 10 mg/day. What we observed is the fall itself. Whether the corticosteroid caused it is not something a single uncontrolled episode can establish, and the third episode had settled on its own, so the two readings remain open. At the most recent determination, on day +491, ALT was 26 IU/L, within the reference range and below the patient’s own pre-treatment mean, and FIX activity was 58.3 IU/dL. The fourth episode has therefore resolved, and follow-up continues. Table 2 summarises the four episodes and the preceding transient elevation, and Figure 2 shows the combined trajectory of FIX, ALT and PDN.

Episode	Timing	Peak ALT	Concomitant FIX	Corticosteroid at the time	Action	Outcome
Prelude to the first episode	D+27	51 IU/L (1.3×ULN)	31.3 IU/dL, no fall	None	Observation	ALT 41 IU/L at 48 h
First	D+34	48 IU/L (1.2×ULN; 1.3× baseline)	Fall from 31.3 to 26.9 IU/dL (-14%)	None	Prednisone 60 mg/day	ALT returned to normal within seven days; FIX rose to 66.7 IU/dL in month 4
Second	D+105 to D+112	74 IU/L (1.9×ULN; 2.0× baseline)	Stable, 49.3-53.3 IU/dL	Prednisone 15 mg/day during tapering	Re-escalation to 60 mg/day for four weeks, followed by slower tapering	ALT falling at two weeks; no second-line treatment
Third	D+380, 3 July 2026	72 IU/L (1.8×ULN; 2.0× baseline)	Rise to 65 IU/dL	None; withdrawn on D+369	Observation	ALT 41 IU/L on D+391; fluctuations to 63 and 62 IU/L on D+398 and D+405, respectively, without treatment; 42 IU/L on D+433
Fourth	D+460, 21 September 2026	88 IU/L at seven days (2.2×ULN; 2.4× baseline)	Fall from 54 to 48 IU/dL (-11%), with 50.8 IU/dL at seven days	None	Prednisone 15 mg/day for seven days, then 10 mg/day	ALT 50 IU/L and FIX 64.8 IU/dL on D+474; resolved, with ALT 26 IU/L and FIX 58.3 IU/dL on D+491

TABLE 2: Chronology of the ALT elevations, immunosuppressive treatment and outcome.

The patient’s baseline ALT was 36.6 IU/L.
ALT, alanine aminotransferase; D, day after infusion; FIX, factor IX; ULN, upper limit of normal, 40 IU/L

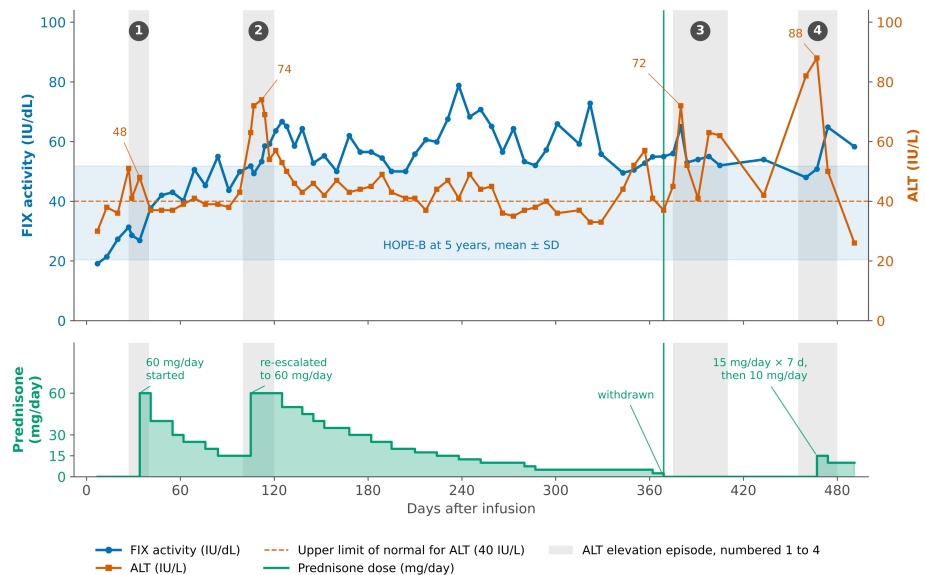


FIGURE 2: Longitudinal trajectory of FIX activity, ALT and prednisone dose after the infusion of etranacogene dezaparvovec.

FIX activity on the left axis, ALT on the right axis and the daily prednisone dose on the lower panel, from the infusion (D0, June 2025) to day +474. The four grey vertical bands, numbered 1 to 4, mark the ALT elevation episodes and run through both panels so that each episode can be read against the corticosteroid dose at that moment. The peak ALT of each episode is labelled on the curve. The horizontal dashed line is the upper limit of normal for ALT, 40 IU/L. The blue horizontal band is the mean $\pm$ SD of factor IX activity at five years in HOPE-B, 36.1 ± 15.7 IU/dL. Every change in corticosteroid dose is labelled in the lower panel: 60 mg/day started on D+34, re-escalation to 60 mg/day on D+105, complete withdrawal on D+369, marked also by the vertical green line, and the short course of 15 mg/day started on D+467 followed by 10 mg/day.

Image credit: Manuel R. López.

ALT, alanine aminotransferase; D, day after infusion; FIX, factor IX; SD, standard deviation

Verification of the funding milestone and cost offset

Maintenance of the clinical response and of FIX activity allowed the first-year efficacy milestone to be verified on VALTERMED, so the criterion for the corresponding payment was met [10]. It is an administrative detail with consequences. The scheme makes part of the initial durability risk contingent on the clinical result.

The comparator arm, that is, the prophylaxis the patient was actually receiving, amounts to about €175,500 a year, counting drug and bleed costs. Under the staggered scheme and with a 3% discount rate, the cumulative cost of GT should stay below that of prophylaxis over the first five years and exceed it transiently when the last instalment is paid in month 60. It would then fall below it again from year 12. The break-even point in present value would lie between years 11 and 12. With a response duration of 5, 7 or 10 years, GT does not offset the cost of the previous prophylaxis. At 15 years the estimated saving would be about €460,000 and at 20 years about €990,000 (Table 3, Figure 1). In a conservative scenario of a single upfront payment of €1.9 million, break-even would be reached around year 13.

Response duration (years)	Saving (+) or additional cost (-) in present value at 20 years
5	-€870,000
7	-€570,000
10	-€160,000
12	+€100,000
15	+€460,000
20	+€990,000

TABLE 3: Sensitivity of the cost offset to the durability of the response.
Perspective of the Spanish National Health System, 20-year horizon, 3% annual discount rate. The comparator is the patient’s own prophylaxis before gene therapy: 234,000 IU/year of rFIXFc at €0.73/IU plus €2,820 per bleed at an annualised bleeding rate of 1.66, about €175,500 a year. The gene therapy arm comprises an initial payment and payments conditional on response at 12, 24, 36, 48 and 60 months; loss of response is assumed to return the patient to the same prophylaxis. The terms of the agreement are confidential, so the split between instalments is modelled, constrained by the published total and by the verification milestones. Administration and monitoring costs are excluded, and no utilities or quality-of-life data are used. The duration of response is the one-way sensitivity analysis shown in the table. These are projected figures under each scenario, not savings that have been realised.

These figures indicate how long the response would have to last to offset the previous prophylaxis, not how long it will last. A follow-up of 15 months does not allow individual durability to be projected. The full economic analysis, with its parameters and its sensitivity analysis, is presented in detail in separate work by our group. These projections also start from a local payment model, which limits their extrapolation to other markets.

Discussion
Efficacy was as expected

The haemostatic result is in line with what has been published since the pivotal trial. A single infusion normalised FIX activity, and there were no bleeding episodes over 15 months in a patient who had continued to experience bleeding episodes despite optimised prophylaxis and good adherence. The values sit at the favourable end of the expected response, above the HOPE-B mean [7]. That fits his profile. A low previous trough, below 8%, may be associated with a greater absolute haemostatic benefit. We put this forward as a hypothesis, not as a selection criterion. Candidacy for GT also depends on bleeding phenotype, treatment burden, liver status, previous anti-AAV immunity, comorbidities and patient preference [4].

Liver course is what this case adds

The first two episodes differed in timing and, probably, in mechanism. The first, in week 5, came with a fall in FIX. This is consistent with destruction of transduced hepatocytes by cytotoxic T lymphocytes directed against capsid peptides [16]. It responded quickly to full-dose prednisone and reproduced the usual pattern of the trial [7]. The second, in week 16, occurred without a significant fall in FIX despite the enzyme rise. In fact, FIX levels fluctuated but always stayed above 49 IU/dL. One possible explanation is a low-grade residual immune response, unmasked when corticosteroid suppression fell below a critical threshold. That response would not reach the cytotoxic mass needed to destroy transduced hepatocytes. We cannot confirm this without capsid-specific T-cell studies or a liver biopsy, and other explanations remain open, including intercurrent causes of enzyme rise unrelated to the vector. We set the mechanism out as a hypothesis, and the distinction between what we measured and what we suspect should be kept in view throughout. Recent human data also indicate that immune activation and endoplasmic reticulum stress may coexist during the acute episode [17].

The last two elevations illustrate the other side of the problem. They appeared late, off corticosteroids and without a significant fall in FIX. The third came down in 11 days and went on fluctuating for another month, with no intervention from us. The fourth kept rising until day 7 of the episode, with FIX falling by 6 IU/dL without leaving the non-haemophilic range, and it settled with a short, low-dose course of prednisone. The pattern seems less suggestive of vector-related immune-mediated hepatocellular damage, which usually comes with loss of expression. In the first French real-world experience [18], three patients were treated, and none of them needed corticosteroids. Two had transient transaminase elevations, and in both, the rise in ALT came with a simultaneous rise in FIX. Our conservative approach matches theirs. The difference lies in the timing, considerably later in our case. Taken together with our last two episodes, this remains an exploratory signal. It may support close observation in selected cases, but it does not yet license withholding corticosteroids as a general rule. The fourth episode illustrates that well. Observation no longer seemed

sufficient when ALT kept rising, and the short course at 15 mg/day was chosen with no published criterion behind it. It worked, and FIX rose, but with a single episode, we cannot rule out that ALT would have come down just the same untreated.

Cost of prolonged monotherapy

Total corticosteroid exposure far exceeded the maximum duration described in HOPE-B: 335 days compared with 130 [7]. The adverse effects of corticosteroids are a recognised burden of this strategy. Here they translate into 5 kg of weight gain and 10 months of prophylaxis against *Pneumocystis*. That raises a question. When does this cumulative cost justify adding a steroid-sparing agent, even in a patient who is responding? The question has no answer in trial data. In haemophilia A, mycophenolate mofetil and tacrolimus have been used as rescue therapy after failure of corticosteroid monotherapy [19]. In HB treated with ED there is no published experience with second-line immunosuppression. In our patient prednisone monotherapy was enough, and we avoided adding drugs whose risk-benefit balance in this setting is unknown.

Intensive monitoring had two sides. It detected transient biochemical changes early, and at the same time it raised the risk of overinterpreting fluctuations of little clinical significance. Several mild ALT elevations resolved or fluctuated without a progressive fall in FIX. In HOPE-B, participants with post-treatment ALT elevation showed a mean FIX below that of those who did not have one, always within the therapeutic range and with no formal statistical comparison. It is therefore not a validated predictor [6,7]. Our patient stayed above 48 IU/dL from month 4 onwards. The summary of product characteristics already recommends measuring AST and CPK in parallel and using a single laboratory [13]. We would add that the decision to start or prolong corticosteroid treatment should rest on the joint trajectory of ALT and FIX and on the clinical context, not on an isolated value.

The interpretation of ALT deserves a methodological caveat. The patient worked night shifts^{*,**} and samples were always drawn at the end of the shift, after 12 hours of fasting and without prior rest. ALT shows marked circadian variation [20]. Non-standardised sampling may have added variability to the values, although it does not explain the episodes. The practical implication is simple. The timing of blood draws should be standardised in the follow-up of these patients.

What the outcomes-based agreement adds

The verification of the first-year milestone on VALTERMED is, as far as we know, one of the first real-world descriptions of how an agreement of this kind behaves in GT [10]. The mechanism ties spending to the clinical response over the 5 years in which instalments remain outstanding. Its reach should not be overstated. Once the last instalment of month 60 is paid, the payer has disbursed almost the whole cost. A later loss of expression would fall on the payer, with the added cost of restarting prophylaxis. The scheme shares the initial durability risk, not that of the full horizon. Even so, few health systems have a public registry linking payment to outcome over that period.

Limitations

This report describes a single patient. The results are not generalisable and should be read as hypothesis-generating. Follow-up is 15 months. The saving is projected under each scenario, not realised, and it should not be read as a demonstrated economic benefit. The break-even point lies several years in the future. There are no quality-of-life or utility data, so the analysis is a cost-offset and not a cost-utility analysis. The baseline period was retrospective, with possible under-recording of bleeds. The long-term projections are deterministic. The modelled distribution of payments determines the break-even point. The biphasic pattern of the first two episodes and their management were the subject of a previous letter to the editor [11]. Preliminary economic results were presented as meeting abstracts. Here they are brought together with the complete 15-month follow-up, which includes corticosteroid withdrawal, the last two ALT elevations and the reassessment of joint health. The ALT of the fourth episode has normalised, but whether the short corticosteroid course brought that about cannot be established from one uncontrolled episode. Capsid-specific T-cell studies and liver biopsy were not available, so the mechanistic hypotheses remain unverified.

Conclusions

At 15 months after a single infusion, the patient maintains FIX activity in the non-haemophilic range, has not bled, and has not needed to infuse FIX concentrate since the day after GT. Established arthropathy has not progressed, at least from the ultrasound standpoint. On the other side of the balance sit an 11-month corticosteroid course and four ALT elevations, two of them treated with full doses and the fourth with a short, low-dose course. This scenario has not been considered in any protocol. In our view it amounts to an unmet need in relation to GT with ED.

Three practical lessons come out of this case. Liver surveillance should not end at week 12 in someone who has already had a treated episode. A rise in ALT during the taper deserves attention, even if FIX stays stable. And a late rise, off corticosteroids and with FIX preserved, may be worth observing before treating, at least while FIX does not fall and ALT does not keep rising. We put that third one forward with particular caution.

The fourth episode marks its limit: ALT kept rising, and we ended up treating it. None of the three can be turned into a rule from a single patient; none of them should displace the guidance in the summary of product characteristics, and all three would need testing in larger series before they could inform practice. Hence the importance of reporting these cases. As more patients come to this therapy, patterns of liver disturbance are likely to emerge that call for different management. HB is uncommon and real-world experience with ED remains limited. As the number of infused patients grows, so will the probability of situations that current protocols did not foresee.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hospital Universitario Alvaro Cunqueiro issued approval N/A. In accordance with the policy of our institution, the retrospective description of an individual case does not require review by the Clinical Research Ethics Committee (CEIm). The report was prepared in accordance with the Declaration of Helsinki. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors used Google Gemini (version 3.5 Flash-Lite, Google LLC, Mountain View, CA) during the preparation of this manuscript for drafting assistance, for translation of the text from Spanish into English, and for formatting the manuscript to the journal's style. No content was generated without author oversight: the authors reviewed and edited all output, verified every clinical figure against the source records, and take full responsibility for the content of this publication.

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