

Gene therapy — new treatment paradigm and challenges for hemophilia B

Journal:	*The Innovation Medicine*
Manuscript ID	TIME-2026-0121.R2
Manuscript Type:	Commentary
Keywords:	gene therapy, hemophilia B, etranacogene dezaparvovec

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Outcome Parameter	**HOPE-B (Etranacogene Dezaparvovec)**		**BBM-H901 (Dalnacogene Ponparvovec) (China)[4]**		**Notes**
Study phase & duration	Phase 3, 5-year follow-up (n=54)		Phase 3, 52-week primary + long-term (n=10, median 210 weeks)		—
Number of Participants	n=54		Phase 1 pilot (n=10), Phase 1-2 (n=6), Phase 3 (n=26)		—
FIX:C at each timepoint	**Median (Min,Max) IU/dL**	**Mean (SD) IU/dL**	**Median (Min,Max) IU/dL**	**Mean (SD) IU/dL**	HOPE-B used One-Stage SynthAsil Method, and BBM-H901 used One-Stage ActinFSL Method. They cannot compare directly. ActinFSL/SynthAsil≈0.61~0.89.
Month 12	39.9 (5.9, 113.0) n=54	41.5 (21.7) n=54	36.5 (1.0,141.9) n=42	42.3 (29.8) n=42	
Month 18	33.6 (4.5, 122.9) n=54	36.9 (21.4) n=54	-	-	
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Month 36	-	-	42.2 (2.0,93.3) n=10	44.2(27.0) n=10	
Month 48	-	-	36.3 (2.0,61.2) n=7	37.1(19.1) n=7	
Month 60	35.5 (4.2, 74.5) n=52	36.1 (15.7) n=52	37.2 (35.0,39.4) n=2	37.2(2.2) n=2	
ABR reduction vs lead-in	63% (4.16 → 1.52)		88% (ABR at week 52 vs historical prophylaxis threshold of 5.0)		HOPE-B: adjusted difference; BBM-H901: superiority vs pre-specified threshold
Prophylaxis discontinuation	94% (51/54)		100% (26/26 in Phase 3)		—
Key safety signal	Transaminitis (11/54), all resolved with steroids		Transaminitis (7/26), resolved with intensified immunosuppression		Both show the elevation of ALT has correlation with early FIX:C decline
Regulatory status	FDA & EMA approved (2022–2023)		NMPA approved (2025)		Timeline reflects real-world rollout divergence

Gene therapy — new treatment paradigm and challenges for hemophilia B

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Regular replacement therapy with intravenous infusion of coagulation factor IX concentrates or non-factor agents has long been the standard of care of hemophilia B (HB). Nevertheless, the enduring burden of lifelong therapy, the persistent threat of breakthrough bleeding, and the suboptimal quality of life collectively provide strong impetus for developing curative therapeutic options. Clinical cure refers to the complete restoration of factor IX activity (FIX:C) to normal levels, with permanent freedom from further replacement therapy, which is the ultimate goal of HB treatment. As for now, the recent five-year end-of-study analysis of the HOPE-B trial published in the New England Journal of Medicine shows that the AAV5-FIX-Padua gene therapy etranacogene dezaparvovec can maintain stable FIX:C and significantly reduce annualized bleeding rate (ABR) during long-term follow-up, can be considered as functional cure of HB.[1]

Early gene therapy for HB used the wild-type factor IX gene, but yielded suboptimal therapeutic outcomes, with FIX:C increasing by only 2-11%.[2] Subsequently, with the discovery that the Padua variant of factor IX has higher activity, most later gene therapy approaches adopted this mutant gene, thereby substantially improving therapeutic efficacy. Recently, Steven W. Pipe and colleagues presented the five-year efficacy and safety results follow-up from the phase 3 HOPE-B study evaluating etranacogene dezaparvovec-the first gene therapy for HB to receive approval from both the US Food and Drug Administration and the European Medicines Agency. In this phase 3 trial, 54 patients with severe or moderately severe HB (FIX:C$\leqslant$2IU/dl) were given a single infusion of etranacogene dezaparvovec at a dose of 2×10^{13} vector genomes per kilogram of body weight (vg/kg). This therapy employs an AAV5 vector designed to deliver FIX Padua variant to hepatocytes. Five years after treatment, participants maintained a stable mean FIX:C of 36.1 IU/dl (SD 15.7) measured with one-stage (OS) SynthASil method (the same below), an outcome that remained robust even in the presence of anti-AAV5 neutralizing antibodies. Over the same five-year period, the ABR for all bleeding events declined from 4.16 during the lead-in phase to 1.52, representing a 63% reduction. Moreover, 51/54 patients (94%) no longer required prophylaxis, and the overall use of exogenous FIX concentrates decreased by approximately 96%. Only three participants failed to demonstrate FIX expression following gene transfer. One individual experienced a severe infusion-related reaction and consequently received only 10% of the intended vector dose. Another had a pre-existing anti-AAV5 neutralizing antibody titre exceeding 3000. The third initially responded to treatment but resumed FIX prophylaxis 29 months after gene therapy because FIX:C had fallen to 3.6 IU/dl in association with recurrent bleeding. The durability of therapeutic benefit remains one of the most closely watched outcomes in gene therapy. Notably, the mean FIX:C at two years in the HOPE-B phase 3 trial was 36.7 IU/dl (SD 19.0), indicating that factor levels remained essentially stable over the subsequent three years and demonstrating stable, clinically meaningful long-term expression. Safety is also a major concern in gene therapy. The HOPE-B study showed that the vast majority of treatment-related adverse events occurred within six months after gene therapy, with liver function abnormalities being the most common, reported in 11 participants. Among them, 9 received glucocorticoid treatment, and liver function returned to normal in all affected individuals.

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However, a certain correlation was observed between liver function abnormalities and an early decline in FIX:C. In addition, no gene therapy-related malignancies, inhibitor development, thrombotic events, or thrombotic microangiopathy were identified.

Accordingly, the 5-year long-term follow-up data from the HOPE-B study demonstrated impressive efficacy and safety. Notably, it pioneered the inclusion of patients with positive anti-AAV neutralizing antibodies, making it the FIX-Padua gene therapy with the most extensive clinical data currently available in Western populations. In parallel, China's HB gene therapy candidate BBM-H901- an approved AAV-FIX-Padua therapy, has generated complementary evidence, further supporting the applicability of this strategy across diverse ethnic groups.

In a phase 1 pilot study of BBM-H901, 10 Chinese participants with severe or moderately severe HB (FIX:C$\leqslant$2 IU/dl) received a single intravenous infusion at a dose of 5×10^{12} vg/kg. After a median follow-up of 58 weeks (IQR 51.5–99.5), the mean FIX:C level increased to 36.9 IU/dL (SD 20.5), measured with OS Actin FSL method. No serious adverse events or grade 3-4 treatment-related adverse events (TEAE) were reported. Two participants (20%) experienced elevations in ALT and AST accompanied by a decline in FIX:C.[3] Building on these findings, phase 1/2 (n=6) and phase 3 (n=26) clinical trials were subsequently conducted.[4] In terms of efficacy, the ABR at week 52 in the phase 3 study was 0.60 (95% CI: 0.18–1.99), representing a marked reduction compared with the predefined superiority threshold of 5.0 (the mean ABR among Chinese patients with hemophilia B receiving prophylaxis). At week 52, the mean FIX:C reached 41.9 IU/dL (SD 28.7) as measured by the OS ActinFSL method (the same below). Notably, as early as day 6 after gene transfer, the mean FIX:C had already peaked at 59.3 IU/dL (SD 34.9), approaching subsequent maximum levels and enabling patients to discontinue replacement therapy rapidly. Based on the result of phase 3 study, BBM-H901 has been approved by the National Medical Products Administration of China (NMPA). Long-term follow-up of the 10 participants in the phase 1 pilot study showed that, at the last visit (median 210 weeks; range 159-270 weeks), 70% maintained FIX:C levels >35 IU/dL, and 40% achieved levels exceeding 55 IU/dL (OS Actin FSL method). Importantly, one participant from the phase 1 study underwent total knee arthroplasty without perioperative exogenous FIX concentrates infusion; intraoperative blood loss was comparable to that of non-hemophilic patients, and postoperative hemostasis was satisfactory.[5] This provides additional real-world evidence supporting the therapeutic efficacy of gene transfer. Regarding safety, the most frequently observed treatment-related adverse event was transient elevation of transaminases.

The five-year end-of-study results from HOPE-B, together with the short- to mid-term data from BBM-H901, collectively suggest that liver-targeting AAV-FIX Padua gene therapy for HB can, through a single administration, enable patients to achieve sustained and stable FIX:C levels approaching those seen in mild hemophilia-or even within the normal range. They all utilize the FIX gene carrying the Padua mutation, with the main difference being the capsid proteins used.

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The AAV5 vector used in the HOPE-B study is a naturally occurring serotype, and its safety and efficacy have been validated through long-term follow-up in more than one hundred patients. Clinically significant CTL-mediated immune responses are rarely observed, and the impact of pre-existing AAV5 antibodies is relatively limited. In contrast, AAV843 is a serotype generated through gene editing of AAV2, with substantially enhanced hepatic transduction efficiency, enabling relatively ideal FIX expression levels to be achieved at a lower vector dose. Reducing the vector dose may help decrease the severity of liver function abnormalities and reduce the need for glucocorticoid therapy. Because patients receiving gene therapy based on the same AAV serotype generally have only one opportunity for treatment, prophylactic glucocorticoids were administered in the BBM-H901 study to maximize patient benefit, and patients who were positive for pre-existing AAV843 antibodies were excluded. The impact of pre-existing AAV843 antibodies on the efficacy of gene therapy remains unclear, and long-term follow-up data are currently insufficient. Therefore, longer-term monitoring is still required, as well as further evaluation of the efficacy and safety of this therapy in antibody-positive patients.

Although the results are encouraging, gene therapy still faces numerous challenges. First, longer-term follow-up is required to verify long-term safety and efficacy. Current trial data suggest a favorable safety profile; however, the potential oncogenic risk associated with low-frequency AAV integration and clonal expansion of hepatocytes requires 10 years or even longer of follow-up for confirmation. A regular liver ultrasound examination and alpha-fetoprotein (AFP) testing are essential. In terms of efficacy, FIX:C has shown a gradual decline during follow-up. In the HOPE-B study, the decline over 2-5 years has been minimal, but longer observation is still needed to further confirm the durability of gene therapy. Second, the target population for gene therapy remains highly restricted. Because hepatotropic AAV vectors are used, patients with abnormal liver function or active liver disease are not suitable candidates for this treatment. Pre-existing AAV antibodies represent another significant influencing factor. Although AAV antibody-positive participants were included in HOPE-B, those with the highest titers demonstrated poorer therapeutic responses. Since multiple gene therapy clinical trials have demonstrated a rapid increase in neutralizing antibody titers to extremely high levels shortly after administration, it is reasonable to assume that, under current circumstances, each patient has only a single lifetime opportunity to receive a given AAV gene therapy product. Although several approaches, including exosome-associated AAV, empty capsid decoys, and plasmapheresis, are being actively investigated in vitro, their translation into clinical practice remains a distant prospect. Therefore, BBM-H901 did not enroll antibody-positive participants. Given that a considerable proportion of individuals in the real world are AAV antibody-positive, this further limits the broad implementation of gene therapy. In addition, the high cost of gene therapy currently restricts access, and only a small number of patients can afford the treatment.

In summary, the five-year final analysis of HOPE-B confirmed that etranacogene dezaparvovec can achieve sustained FIX expression, significantly reduce bleeding rates, and maintain a favorable safety profile, marking a new stage of long-term efficacy in gene therapy for

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HB. Longer-term follow-up data will help provide more definitive evidence regarding both efficacy and safety. It is anticipated that, with further improvements in vector design and reductions in cost, gene therapy will benefit a broader population of patients with HB and has the potential to truly reshape the treatment paradigm for this disease.

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FUNDING AND ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation of China (82470138 X.F., 82430010 Z.L.), National Key Research and Development Program of China (2023YFC2507803 J.M.K., 2023YFC2507802 X.F.), CAMS Innovation Fund for Medical Sciences (CIFMS) (2024-I2M-ZH-016 Z.L.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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