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Adeno-associated virus gene therapy for hemophilia B: a comparative appraisal of the licensed products

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Abstract

Among the inherited bleeding disorders, hemophilia B has become the leading target for adeno-associated virus (AAV) gene therapy. The compact factor IX (FIX) coding sequence, the abundance and durability of hepatocyte-derived FIX expression and the hyperactive FIX-Padua variant together made single-infusion phenotypic correction achievable earlier and more convincingly for FIX deficiency than for factor VIII (FVIII) deficiency. Three FIX-Padua AAV products have reached regulatory approval: etranacogene dezaparvovec, licensed in the United States, Canada and Europe; fidanacogene elaparvovec, initially licensed in the same regions but discontinued worldwide by its manufacturer; and dalnacogene ponparvovec (BBM-H901), licensed in China. This review outlines the biological differences between FVIII and FIX, the immunological and analytical challenges common to all AAV FIX products, and the pivotal trial data for each licensed therapy. Because FIX-Padua activity is reagent dependent, activity is standardized throughout to a single one-stage scale (HemosIL SynthASil), permitting a like-for-like comparison: mean activity 27–55 IU/dL, annualized bleeding rates 0.6–1.5 and reductions in FIX consumption exceeding 90% for all three products, sustained to five years for etranacogene dezaparvovec and six for the fidanacogene elaparvovec phase 1/2a cohort. Only dalnacogene ponparvovec has published data in adolescents. The review compares the three products' capsids, genome configurations, doses, impact of pre-existing anti-AAV immunity and immunomodulation, and weighs their reassuring but surveillance-dependent long-term safety, including the theoretical risk of insertional oncogenesis. Finally, it considers why the clearest efficacy successes have coincided with limited real-world uptake, and what the divergent commercial and regulatory trajectories imply for equitable global access.

Introduction

Hemophilia A and hemophilia B, caused respectively by deficiency of coagulation factor VIII (FVIII) or factor IX (FIX), are clinically almost indistinguishable, but the two deficient proteins differ greatly at the molecular level, and those differences determined which disease was corrected first by a single gene therapy infusion.

Both are X-linked recessive disorders graded as mild, moderate or severe by residual factor activity.[1] Hemophilia A is about five times more common, affecting roughly 1 in 5,000 male births versus 1 in 30,000 for hemophilia B.[2] Factor IX is a compact, 415-amino-acid vitamin K-dependent serine protease synthesized by hepatocytes and circulating at around 5 µg/mL.[3] Factor VIII is a 2,332-amino-acid multidomain glycoprotein synthesized by liver sinusoidal endothelial cells; at only 0.2 µg/mL, 50-fold below FIX, it is secreted inefficiently and depends on von Willebrand factor for stability.[3,4] These differences determine coding-sequence size, target cell, expression kinetics and durability, and the vector dose required for AAV gene transfer.

The most consequential difference is size. The *F9* coding sequence is only about 1.4 kb, whereas full-length *F8* approaches 7 kb, beyond the roughly 4.7 kb an adeno-associated virus (AAV) capsid can package.[5,6] FVIII therefore requires deletion of its dispensable B domain, and even the B-domain-deleted construct fills the capsid to its limit or beyond, constraining regulatory elements and depressing manufacturing yield.[5,7,8] The FIX cassette occupies a fraction of the space and can be delivered as a self-complementary, double-stranded genome that bypasses second-strand synthesis for faster, more efficient expression.[9]

Both disorders are managed by prophylaxis, traditionally by intravenous factor replacement and increasingly by subcutaneous non-factor agents, but every regimen demands lifelong repeated administration, with the burden of venous access, breakthrough bleeding and progressive arthropathy that a single infusion seeks to abolish.[10] Three gene therapy products exploiting the hyperactive FIX-Padua (R338L) variant — a naturally occurring gain-of-function substitution first described in a family with X-linked thrombophilia[11] — have been approved for hemophilia B, and one FVIII gene therapy, valoctocogene roxaparvovec, for hemophilia A; valoctocogene roxaparvovec and fidanacogene elaparvovec have since been withdrawn from all

markets, leaving etranacogene dezaparvovec the only such product available in the West and dalnacogene ponparvovec the only one approved in China.

Methods

This narrative review compares the three licensed FIX-Padua AAV gene therapies (Tables 1 and 2). The authors searched MEDLINE (PubMed) to September 2026, without language restriction, combining hemophilia B, factor IX, gene therapy, adeno-associated virus and FIX-Padua with the individual product names, and hand-searched reference lists, ISTH, EAHAD and ASH proceedings, the assessment documents of the FDA, EMA and China's National Medical Products Administration, and the ClinicalTrials.gov and Chinese trial registries. Prospective studies reporting FIX activity, bleeding or safety outcomes were eligible; preclinical work, case reports and superseded abstracts were not. Fidanacogene elaparvovec is retained because its pivotal-trial data form part of the licensed evidence base and its low dose and distinct capsid inform any comparison of vector and dose.[5,6] Where a product had several reports, the pivotal trial and its most mature follow-up were used; FVIII data are cited only for comparison. Both authors extracted vector and dose, cohort size, follow-up, FIX activity with the assay used, annualized bleeding rate, factor consumption and adverse events, resolving discrepancies against the regulatory documents; data were synthesized narratively.

Because FIX-Padua activity is assay dependent and the trials used different reagents, activity is reported throughout as one-stage clotting activity obtained with the silica-based HemosIL SynthASil aPTT reagent, the central-laboratory reagent in HOPE-B,[12] BENEGENE-2[13] and the dalnacogene ponparvovec phase 3 trial.[14] Where a source reported activity with the ellagic acid-based Dade Actin FSL reagent, the published value is given first and an estimated SynthASil equivalent follows, obtained by multiplying by 1.3.[12,14] That factor rests on paired measurements of the same samples: in HOPE-B the ratio of local Actin FSL to central SynthASil activity was 0.789,[12] and in the dalnacogene phase 3 cohort the two reagents returned 41.9 and 55.1 IU/dL (ratio 0.76),[14] giving a SynthASil-to-Actin FSL ratio of 1.27–1.31, which widens as activity falls.[15] Chromogenic values are approximately half the corresponding SynthASil value.[12] Converted values serve cross-trial orientation only and must not

replace a locally measured result;[16] they are identified as such throughout. Activities are means unless identified as medians or geometric means.

Development of gene therapy for hemophilia B

Gene therapy for hemophilia has been under development for more than three decades. The first preclinical proofs of concept were reported in 1993, a retroviral vector achieving sustained partial correction in factor IX-deficient dogs[17] and factor VIII-secreting fibroblasts persisting in vivo;[18] the earliest clinical attempt, an ex vivo transduced fibroblast implantation, was carried out in China that year.[19] AAV vectors soon became the platform of choice. Intramuscular injection of an AAV-FIX vector produced only local, subtherapeutic expression,[20,21] whereas hepatic-artery infusion of an AAV2-FIX vector achieved transient therapeutic levels but exposed the central obstacle for AAV gene transfer — a capsid-directed CD8 T-cell response that cleared transduced hepatocytes and curtailed expression.[22] Follow-up of that first intravascular cohort now extends to 12–15 years and confirms the safety of hepatic AAV transfer.[23]

In 2011, a single peripheral intravenous infusion of a self-complementary AAV8 vector expressing codon-optimized FIX produced stable activity of an average of 5 IU/dL — the first unequivocally successful systemic AAV gene therapy for hemophilia B[9] — a result confirmed and extended over subsequent follow-up,[24] with sustained clinical benefit now documented to 13 years.[25] Incorporation of the hyperactive FIX-Padua (R338L) variant, pioneered in the SPK-9001 construct, then allowed higher activity from substantially lower vector doses and set the template for every product that followed.[26]

Two further steps translated this proof of concept into the AAV5 platform underlying etranacogene dezaparvovec. AMT-060, pairing an AAV5 capsid with a codon-optimized wild-type FIX cassette under a liver-specific promoter, was given to ten adults at 5×10^{12} or 2×10^{13} vg/kg; it was well tolerated and produced stable but low mild-range activity (means of roughly 5 and 7 IU/dL in the low- and high-dose cohorts) for at least five years.[27] Introducing FIX-Padua into the same vector at 2×10^{13} vg/kg produced etranacogene dezaparvovec (AMT-061): in a three-patient phase 2b study mean one-stage SynthASil activity reached 47 IU/dL at week 26 — five- to sevenfold that of wild-type AMT-060 at an identical dose — with cessation of bleeding and no

need for FIX replacement despite pre-existing anti-AAV5 antibodies,[28] and was maintained at a mean of 45.7 IU/dL at five years, when the trial closed.[29]

Regulatory approvals followed in quick succession: valoctocogene roxaparvovec for hemophilia A (EMA 2022, FDA 2023), etranacogene dezaparvovec for hemophilia B (FDA 2022, EMA 2023 and Health Canada 2023), fidanacogene elaparvovec (Health Canada, FDA and EMA 2024) and dalnacogene ponparvovec (BBM-H901), the first Chinese product (NMPA 2025). The three products differ most fundamentally in their capsids (Table 1).[30] Etranacogene dezaparvovec uses a naturally occurring serotype 5 (AAV5) capsid, phylogenetically distinct from the others[31] and notable for a comparatively low prevalence of neutralizing antibodies[32,33] and for retained efficacy even in their presence.[34,35] Fidanacogene elaparvovec uses AAVRh74var, a bioengineered variant of the rhesus-derived AAVrh74, in the AAV8 clade.[36] Dalnacogene ponparvovec uses AAV843, engineered de novo for liver tropism and lower antibody prevalence in the Chinese population.[37] Because anti-capsid seroprevalence varies by capsid and by geographical population,[32] the capsid determines how many patients are excluded by pre-existing humoral immunity and whether antibody screening is required at all.

A second, universal capsid-related constraint is the capsid-directed T-cell response that emerges in the weeks after infusion, manifests as transient transaminitis, and can destroy transduced hepatocytes unless managed with immunosuppression;[22,33,38] and because the antibodies raised by the vector preclude re-dosing with the same capsid, the initial infusion is in practical terms a single, irreversible opportunity.[39]

A further issue is measurement. Because FIX-Padua has roughly eightfold higher specific activity than wild-type FIX,[11] measured activity exceeds the circulating antigen concentration by about the same factor, so antigen and activity should be interpreted together.[16] Nor is FIX-Padua measured identically by all methods: one-stage and chromogenic assays give discrepant results, and among one-stage assays the value depends on the aPTT reagent, with measured activity varying 1.5- to 1.9-fold across commonly used assays and more at low levels.[12,15,16]

The three licensed products illustrate this directly: the pivotal HOPE-B, BENEGENE-2 and dalnacogene phase 3 trials all used SynthASil as the central one-stage reagent, whereas the fidanacogene and dalnacogene early-phase and long-term cohorts used

Actin FSL, so even nominally one-stage values are not interchangeable; those cohorts therefore understate activity on the SynthASil scale by about a quarter. The correction applies to paired samples, not across cohorts: the two fidanacogene cohorts returned similar one-year values on different reagents, reflecting their size and method of averaging rather than assay agreement.

Which value best reflects clinical reality? No assay has been validated against bleeding outcome after gene therapy, so none is a reference method. Three considerations nonetheless favor one-stage measurement with a silica-activated reagent. The bleeding and consumption outcomes of all three pivotal trials were generated alongside SynthASil activities, so these are the values with a demonstrated clinical correlate.[12] The chromogenic assay tracks the molecule more closely but returns roughly half the one-stage value and would reclassify well-protected recipients as moderately affected.[16] Silica activation is also the most widely used, in about 60% of accredited laboratories,[15,16] so a silica value is the one most centers can reproduce. In practice consistency matters more than the method: a recipient should be followed with one reagent, the value read alongside the bleeding phenotype rather than against a fixed threshold, and any change of reagent recorded.

Etranacogene dezaparvovec

Etranacogene dezaparvovec (AAV5-hFIXco-Padua; developed by uniQure and acquired by CSL Behring) was the first hemophilia B gene therapy, and the first AAV gene therapy for any bleeding disorder, to be licensed. It pairs a naturally occurring AAV5 capsid with a codon-optimized FIX-Padua transgene under a liver-specific promoter, given as a single-stranded genome at 2×10^{13} vg/kg — the highest of the three doses, some 40-fold that of fidanacogene elaparvovec.

The pivotal HOPE-B trial was an open-label, single-arm, multinational phase 3 study in 54 men with FIX activity ≤2 IU/dL, dosed after a lead-in of at least six months on prophylaxis.[40] Uniquely among the three products, it enrolled participants irrespective of pre-existing AAV5 neutralizing antibodies (NAbs), reflecting the relative resistance of AAV5 to moderate humoral immunity. Twenty-one of the 54 participants had detectable NAbs; efficacy was preserved across the titres encountered — up to 1:678 — while the sole NAb-related failure occurred at a markedly higher titre of 1:3,212, at which no FIX was expressed. The label accordingly does not require NAb-negative

status, as its two competitors effectively do,[41,42]. The threshold has since been recalibrated rather than abolished. The HOPE-B titres were generated with an unvalidated clinical trial assay using a seven-point dilution curve; a validated assay with a nine-point curve and an extended linear range has replaced it, on which the 1:678 ceiling corresponds to 1:898 and the failing titre of 1:3,212 to 1:4,417.[43] The European product information accordingly advises that the titre be measured before treatment and that values above 1:898 may impede transgene expression, whereas the US prescribing information specifies no threshold in its indication or patient-selection criteria and leaves testing optional.[41,43] In the primary analysis the adjusted annualized bleeding rate (ABR) for all bleeds fell from 4.19 during lead-in to 1.51 during months 7–18, meeting both non-inferiority and superiority, with mean FIX activity rising by about 36 IU/dL.[40]

Three factors plausibly explain this relative resistance. AAV5 is the most divergent capsid in clinical use, sharing only about 55–60% of its amino acid sequence with the AAV2 and AAV8 clades, so antibodies raised by exposure to the commoner serotypes cross-neutralize it poorly and anti-AAV5 titers, where detectable, are usually low.[32,36] That divergence is more than sequence-deep: AAV5 is most closely related (94% capsid amino acid homology) to a caprine AAV, AAV-Go.1,[44] and so appears to have entered humans from a non-primate host;[31] it differs functionally in step with its position, attaching to N-linked sialic acid rather than heparan sulfate and engaging the first PKD domain of the AAV receptor where AAV2 uses the second and AAV8 uses both.[45] Second, the dose is high, and vector given in antigen excess adsorbs neutralizing antibody in a dose-dependent manner, as capsid-decoy experiments show, up to a ceiling above which transduction cannot be rescued;[46] the HOPE-B pattern corresponds closely to such a ceiling. Third, the assay probably overstates the barrier: transduction-inhibition assays depend on the reagents and the indicator cell line and also detect non-antibody inhibitors, so a measurable titer need not correspond to a block in vivo, and AAV5-FIX vectors transduced the liver in both non-human primates and NAb-positive patients.[47] A phase 3b study confined to NAb-positive patients (NCT06003387) is testing prospectively whether a titer threshold for selection can be defined.

The end-of-study analysis, reported in 2026, is the longest prospective follow-up for any licensed hemophilia B product.[48] Fifty of the 54 participants completed five years

(the four who did not comprised two treatment-unrelated deaths, one liver transplantation and one consent withdrawal). The adjusted all-bleed ABR fell from 4.16 at lead-in to 1.52 during months 7–60 (rate ratio 0.37; 95% CI, 0.18 to 0.76), reaching significance for spontaneous, joint and traumatic bleeds alike, with the annual rate declining progressively to 0.40 in years 4 and 5 (Figure 2A). Mean endogenous FIX activity remained above 30 IU/dL (one-stage SynthASil) throughout, at 36.7 IU/dL at month 24[49] and 36.1 IU/dL at year 5 (Figure 1), independent of baseline NAb status,[34,35] while annualized exogenous FIX consumption fell by 96% (from ≈257,000 to ≈11,000 IU per participant-year, Figure 2C). The two non-responders were the high-titre participant noted above and one who received about 10% of the intended dose; a further participant resumed prophylaxis at ≈30 months. Among the 52 who expressed FIX and stopped prophylaxis, 51 (98%) remained prophylaxis-free at five years, 80% had FIX activity of at least 12 IU/dL (SynthASil), and every bleed subtype was reduced by at least 80%.[48] Freedom from prophylaxis did not require high activity: a minority of participants remained off prophylaxis throughout with activity persisting in the low mild range. Continuous endogenous expression is pharmacologically unlike intermittent replacement, in which a mean value conceals recurrent troughs; a stable 5–10 IU/dL therefore sustains hemostasis better than the same figure reached only as a trough between infusions, and does so uninterrupted and independently of adherence. Continuous hepatic secretion also replenishes the extravascular factor IX pool bound to collagen IV in the subendothelium, which in animal models sustains hemostasis after circulating factor IX has become undetectable.[50] The comparison, moreover, is with severe disease: moving from below 1 IU/dL into the mild range abolishes most spontaneous bleeding, whereas further gains toward normal add benefit mainly for traumatic bleeding. Bleeding phenotype after gene therapy is therefore not a linear function of the measured activity, and the decision to resume prophylaxis is better guided by bleeding and joint outcomes than by an activity threshold alone.

The safety profile matured favorably: of 100 treatment-related adverse events over five years, 91 occurred within the first six months and only five between years 4 and 5. The most common adverse events were an early alanine aminotransferase rise in ten participants, nine of whom received corticosteroids for a mean of about 80 days.

No FIX inhibitors developed, no vector-related hepatotoxicity persisted.[48] Participants are being followed to 15 years in IX-TEND (NCT05962398).

Fidanacogene elaparvovec and its discontinuation

Fidanacogene elaparvovec (formerly SPK-9001 / PF-06838435; developed by Spark Therapeutics and licensed by Pfizer) reaches the same transgene by a different route, carrying a codon-optimized, CpG-depleted FIX-Padua sequence in a bioengineered rhesus-derived capsid (AAVRh74var) as a single-stranded genome. Its defining feature is dose: 5×10^{11} vg/kg, roughly one-fortieth that of etranacogene dezaparvovec and among the lowest effective doses reported. Dose is not, however, a function of capsid potency and the Padua variant alone: fidanacogene elaparvovec and dalnacogene ponparvovec are produced in mammalian HEK293 cells, whereas etranacogene dezaparvovec is manufactured in the baculovirus–Sf9 insect-cell system (Table 1), and vector produced in insect cells suffers greater vector-genome loss and epigenetic silencing, and hence lower per-genome potency, than the same construct produced in mammalian cells.[51]

A phase 1–2a trial achieving sustained mild-to-normal FIX activity at this dose[26] preceded the pivotal BENEGENE-2 trial, which enrolled 45 men with FIX ≤2 IU/dL, again with a prospective prophylaxis lead-in.[13] The all-bleed ABR fell from 4.42 to 1.28 (a 71% reduction, meeting non-inferiority and superiority), infusions fell by 92%, and bleeding was eliminated in 64% of participants versus 29% on prophylaxis (Figure 2A, 2B).[13] Mean one-stage SynthASil FIX activity was 26.9 IU/dL at 15 months and 26.6 IU/dL at 24 months,[13] the longest interval reported in the pivotal trial; six participants (13%) had returned to continuous prophylaxis by month 24. In the phase 1/2a cohort, monitored with Actin FSL,[52] expression remained stable for six years, at a mean of 26.1 IU/dL in the 11 participants still followed.[53] Safety was that of the class — transaminase elevations managed with corticosteroids, without inhibitors or thrombosis. Fifteen-year follow-up is planned.

Its subsequent course, however, illustrates the commercial fragility of the field. In February 2025, less than a year after US approval, the manufacturer discontinued fidanacogene elaparvovec worldwide, withdrawing its Japanese submission and UK appraisal and citing limited interest from patients and clinicians.[54] No patient is reported to have received the product commercially before its withdrawal. The

withdrawal reflected a weaker competitive profile — etranacogene dezaparvovec achieved a higher mean FIX activity (37 versus 27 IU/dL, both by SynthASil) — and the difficulty of delivering and reimbursing a very high-cost one-time therapy, rather than any failure of the science.[6]

Dalnacogene ponparvovec (BBM-H901)

The third licensed product, and the first hemophilia gene therapy developed and approved in China, is dalnacogene ponparvovec (BBM-H901), developed and manufactured by Belief BioMed, which took over its commercialization in August 2026 when its partnership with Takeda China ended,[55] and approved by China's National Medical Products Administration (NMPA) in April 2025 for moderate-to-severe hemophilia B and in Macao in March 2026. It too delivers a FIX-Padua transgene but differs in two respects: a distinct bioengineered capsid, AAV843, selected partly for lower pre-existing NAb prevalence in the Chinese population; and a CpG-reduced sequence packaged as a double-stranded (self-complementary) genome under a liver-specific promoter.[14] The double-stranded configuration bypasses second-strand synthesis and gives unusually rapid onset, with activity detectable as early as three days, faster than the single-stranded Western products. Its dose, 5×10^{12} vg/kg, is intermediate between the other two.

The program began with a single-center, investigator-initiated phase 1 pilot in ten adults, with a distinctive immunomodulatory strategy: prophylactic glucocorticoids begun about a week before infusion, pre-empting rather than reacting to the capsid-directed response that drives transaminitis.[37] Mean FIX activity of around 37 IU/dL was achieved over the first year (Actin FSL; ≈48 IU/dL SynthASil-equivalent); at a median follow-up of roughly four years, four of the ten participants maintained activity above 50 IU/dL and five between 10 and 50 IU/dL (Actin FSL), all nine evaluable participants remaining free of bleeding,[14] one having earlier undergone total knee arthroplasty without factor cover.[56]

The registrational data (2025) comprised a dose-confirmation phase 1/2 study in six participants and a phase 3 trial in 26.[14] In the phase 1/2 study no dose-limiting toxicity occurred and the primary endpoint was met; mean FIX activity reached 59 IU/dL at 52 weeks (Actin FSL; ≈77 IU/dL SynthASil-equivalent), no participant bled, and all six completed 104 weeks at which the median was 46 IU/dL and the mean 58.4 IU/dL

(Actin FSL; ≈60 and ≈76 IU/dL SynthASil-equivalent).[14] At 52 weeks the phase 3 cohort achieved a mean ABR of 0.60 (95% CI 0.18–1.99), the upper limit well below the pre-specified superiority margin of 5.0 (the background rate assumed for conventional prophylaxis in China), and mean FIX activity of 55.1 IU/dL by SynthASil (41.9 IU/dL by Actin FSL) — the highest of the three and directly comparable, having been obtained with the same reagent (Table 3, Figure 1) — while annual FIX infusions fell from 58.2 to 2.9 and 81% of participants were bleed-free (Figure 2B). By week 52, 92% of participants had FIX activity above 5 IU/dL and every participant had zero target joints, from 41% at baseline.[14] No grade 4 or serious adverse events and no FIX inhibitor occurred; transaminitis, all CTCAE grade 1–2, arose in seven of the 26 participants (27%) and resolved without additional immunosuppression in all but one.[14]

A single participant (4%) — the only one not given prophylactic prednisone, owing to recent duodenal-ulcer bleeding — expressed no vector-derived FIX despite salvage immunosuppression and resumed prophylaxis at week 38. Non-response here is therefore best read as an unopposed capsid-directed immune response, mechanistically distinct from the two failures in HOPE-B, which followed a high pre-existing anti-AAV5 titre and an incomplete dose. All three illustrate the narrow margin by which a single, non-repeatable infusion can fail. BBM-H901 holds FDA orphan-drug designation and EMA advanced-therapy-medicinal-product classification but remains licensed only within Chinese jurisdictions.

The program has since extended to adolescents. In a multicenter phase 1 trial (NCT05709288), 11 participants aged 12–18 years with FIX ≤2 IU/dL received the same dose under prophylactic glucocorticoids.[57] No dose-limiting toxicity occurred, mean FIX activity at 52 weeks was 41.8 IU/dL (SD 30.1, SynthASil) and the mean ABR fell from 13.9 to 0.5; one participant had an alanine aminotransferase rise to 197 U/L that normalized within four weeks of immunosuppression, and the commonest adverse events were corticosteroid related.[57] These are the first prospective data for any FIX-Padua product outside adulthood. Mean activity was nonetheless lower, and far more variable, than in the adult phase 3 cohort at an identical dose and on the same reagent, so durability in a still-growing liver remains open.

Convergence and divergence across the three products

Vector and genome design. All three deliver the identical FIX-Padua transgene through different capsids — the natural AAV5 for etranacogene dezaparvovec, the bioengineered AAVRh74var and AAV843 for the other two. Genome configuration divides them more sharply: the Western products are single-stranded, whereas BBM-H901 is double-stranded and expresses faster, an advantage of unproven clinical value but plausible for a patient bleeding at the time of dosing.

Dose. Effective doses span an approximately 40-fold range.

Lower doses reduce capsid antigen load, manufacturing cost and, in principle, dose-dependent hepatotoxicity, yet the highest-dose product carries the longest and most reassuring safety record.

Pre-existing immunity. Etranacogene dezaparvovec is the only one of the three that can be given regardless of pre-existing NAbs, sparing the eligibility screening that excludes many candidates for the others; fidanacogene elaparvovec requires AAVRh74var-negativity and BBM-H901 a low or absent anti-AAV843 titer. Because seroprevalence varies geographically, a capsid optimized for one population may not carry its advantage to another.

Immunomodulation. The Western products treat the capsid-directed response reactively, starting corticosteroids when transaminases rise or FIX falls; BBM-H901 used prophylactic prednisone — 1 mg/kg/day (maximum 80 mg/day) tapered over about eight weeks — begun seven days before infusion in the pilot and phase 1/2 studies but only one day before in the registrational phase 3 study and the approved regimen.[14,58] Pre-emptive immunosuppression may better protect newly transduced hepatocytes but exposes every patient to corticosteroid toxicity; no head-to-head data compare the two strategies. Across the class the transaminitis is transient, mild-to-moderate and steroid-responsive, and reactive corticosteroids were needed in roughly 17% and 62% of etranacogene and fidanacogene recipients, whereas all BBM-H901 recipients received prophylactic prednisone and about 12% required additional immunosuppression.[14,59] Mechanistic support comes from a parallel Chinese hemophilia A program, in which prophylactic prednisone with tacrolimus suppressed capsid-directed CD8 T-cell responses.[60]

Efficacy and durability. Cross-trial comparison remains indirect given differences in populations, doses, vector manufacturing and follow-up, which should temper any ranking by reported activity even now that it is expressed on a common assay scale (Figures 1 and 2). With that qualification, all three convert a severe or moderately severe phenotype into a mild or normal one (Table 2). Etranacogene dezaparvovec has the most mature data in a full cohort; the BBM-H901 pilot and the fidanacogene phase 1/2a cohort offer multi-year and six-year data in few patients; and fidanacogene elaparvovec's planned 15-year follow-up will now accrue only from trial participants. The licensing trials were confined to adults, and the only published data below 18 years are those for dalnacogene ponparvovec at one year.[57]

Safety, integration and the contrast with factor VIII

FIX and FVIII gene therapy behave very differently. FIX gene therapy produces comparatively stable expression — mean endogenous FIX maintained near 36 IU/dL, within the mild range, for five years[48] — whereas FVIII gene therapy shows supraphysiological but waning expression: in the phase 3 AFFINE study a mean of 51 IU/dL at 15 months concealed a range from below 1 to almost 250 IU/dL, transient activity above 150 IU/dL was recorded in 49% of dosed participants, of whom 31% were given prophylactic direct oral anticoagulants, and inhibitor formation has been reported in one participant — events essentially unseen after FIX gene therapy.[61] These divergent trajectories express the molecular differences outlined above and explain why hemophilia B has remained the better-validated target.

The theoretical risk of insertional mutagenesis and hepatic oncogenesis has attracted close scrutiny, particularly after reports of integration near growth-related genes in animal models and of AAV sequences at recurrent integration sites in some human hepatocellular carcinomas.[62] A neuroepithelial tumor has since been reported after intracisternal AAV delivery for a metabolic disorder, with the vector integrated within it — a different tissue and route, but a human instance of integration in a malignancy.[63] A second case followed: a *GLI1*-altered paraspinal neoplasm in a 3-year-old boy 26 months after intravenous AAVrh.10 gene therapy for Krabbe disease, with a rearranged, transgene-less vector fragment integrated into *GLI1* intron 1.[64] In both tumors a subgenomic fragment carrying a CAG promoter-enhancer and the chicken β-actin splice donor activated a developmental transcription factor, and both children

had undergone cord-blood transplantation before gene transfer; neither administered lot was available for sequencing. The liver-specific cassettes used in hemophilia carry no β-actin splice donor, so the determinant may be cassette design rather than AAV integration itself. The accumulated hemophilia data are reassuring. Over five years of HOPE-B follow-up three malignancies arose — a hepatocellular carcinoma, a schwannoma and a myelodysplastic syndrome — yet molecular analysis established in every case that the tumor was unrelated to vector integration,[48] the hepatocellular carcinoma in a dedicated integration analysis.[65] In the clinical FVIII program, integration-site sequencing of liver biopsies found integration to be infrequent and sporadic, orders of magnitude below the background somatic mutation rate and without evidence of pathological clonal expansion.[61,66,67] Malignancies will nonetheless arise in an aging treated population; causality should be attributed only after molecular interrogation, not by temporal association, and long-term surveillance remains appropriate given the permanence of the intervention.[68,69]

Access, economics and equity

A single infusion converts a lifelong prophylactic burden into years of near-normal hemostasis, but the commercial reality has been less encouraging. The withdrawal of fidanacogene elaparvovec within a year of approval reflects pressures bearing on the whole class: price, residual uncertainty about the ultimate duration of benefit, the emergence of effective and far less disruptive subcutaneous non-factor prophylaxis, and the operational demands of delivering, monitoring and reimbursing a one-time therapy[6] have together slowed uptake even where products are licensed and funded. Both Western products carried a list price of about US$3.5 million per dose, fidanacogene elaparvovec being valued at about CAD 4.8 million in the Canadian reimbursement review.[70,71] Dalnacogene ponparvovec launched in July 2025 at CNY 93,000 (≈US$13,000) per vial, dosed by weight, with a charitable program capping individual expenditure at 30 vials, about CNY 2.79 million (≈US$390,000).[55] Even that proved unaffordable: no commercial dose was given in the first year, the patient price was reduced in June 2026 to about CNY 1.39 million (≈US$195,000) — roughly a twentieth of the Western list price — and the first commercial prescription followed in September 2026.[55,72] To standardize this delivery, formal frameworks have emerged: the first WFH AAV gene therapy guidelines (2025), which adopt a living-guideline

model;[73] the UKHCDO taskforce guidance for routine adult practice;[74] the comprehensive care pathway of the ISTH SSC Working Group on Gene Therapy;[75] the EAHAD Gene Therapy Working Group's qualification criteria, which define accredited "hub" centers for administration and certified "spoke" centers for shared monitoring;[76] and, in China, a parallel national guidance for BBM-H901.[58]

Against this background the Chinese approval of BBM-H901 carries significance beyond its clinical data. China has a large hemophilia population in which diagnosis has been late, prophylaxis under-accessed and quality of life correspondingly low;[77,78] the pivotal trial itself took a background annualized bleeding rate of about 5 on conventional prophylaxis as its comparator.[14] The rapid uptake of subcutaneous non-factor prophylaxis there — most clearly for emicizumab in hemophilia A,[79] with rebalancing agents for hemophilia B now approved in the United States and Europe — means the competition that has slowed gene-therapy adoption in the West is emerging in China too. A regionally developed product reached this population with a capsid tailored to local seroprevalence and a price matched to its market; whether that model proves sustainable, and whether BBM-H901 is approved outside China, remains to be seen. The near-simultaneous discontinuation of one product in the West and launch of another in the East reflects the unresolved tension between established efficacy and equitable, durable, affordable access.

Conclusion

Hemophilia B remains one of the clearest successes of AAV gene therapy. That position rests on the molecular characteristics of factor IX rather than on any clinical difference from hemophilia A — a compact coding sequence, an abundant hepatocyte-derived protein and a hyperactive naturally occurring variant. The comparison of the three licensed products shows that the same therapeutic concept can be realized through markedly different capsid, genome, dose and immunomodulation choices that nonetheless converge on the same mild-to-normal phenotype. The five- to 13-year data across AAV FIX gene therapy leave little doubt that the biology works; the challenge is whether health systems, manufacturers and clinicians can deliver these therapies to the patients who stand to benefit. Further progress therefore depends less on the next capsid than on the economics, logistics and equity of access.

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Table 1. Characteristics of the three licensed FIX-Padua AAV gene therapies for hemophilia B

Characteristic	Etranacogene dezaparvovec[40,48]	Fidanacogene elaparvovec[13,26]	Dalnacogene ponparvovec (BBM-H901)[14,37]
Developer / Licensee	uniQure / CSL Behring	Spark Therapeutics / Pfizer	Belief BioMed (Takeda China until 2026)
Production platform[5]	Baculovirus / Sf9 insect cells	HEK293 cells (mammalian)	HEK293 cells (mammalian)
Capsid	AAV5 (naturally occurring serotype)[31-33]	AAVRh74var (bioengineered)[36]	AAV843 (bioengineered)[37]
Genome	Single-stranded	Single-stranded	Double-stranded (self-complementary)
Transgene	Codon-optimized Not CpG-reduced FIX-Padua (R338L)	Codon-optimized CpG-reduced FIX-Padua (R338L)	Codon-optimized CpG-reduced FIX-Padua (R338L)
Promoter	Liver-specific	Liver-specific	Liver-specific
Dose (vg/kg)	2×10^{13}	5×10^{11}	5×10^{12}
Pre-treatment anti-capsid NAb testing (label requirement)	No NAb-negativity required. EU product information advises pre-treatment titer measurement and notes reduced expression above 1:898 on the validated assay (≡1:678 on the trial assay); no threshold in the indication or patient-selection criteria of the US label[40,41,43]	Required; treatment restricted to patients negative for anti-AAVRh74var NAb by an approved companion diagnostic[42]	Required; anti-AAV843 NAb titer below 1:5[14,37]

AAV, adeno-associated virus; CpG, cytosine–phosphate–guanine dinucleotide; FIX, factor IX; HEK293, human embryonic kidney 293 cells; Sf9, Spodoptera frugiperda 9 cells; vg/kg, vector genomes per kilogram. Neutralizing antibody (NAb) titers are

assay-specific and are not comparable between products. In China, dalnacogene ponparvovec is approved as bopaidakeji injection.

Table 2. Comparison of the three licensed FIX-Padua AAV gene therapies for hemophilia B.

Parameter	Etranacogene dezaparvovec[40,48]	Fidanacogene elaparvovec[13,26]	Dalnacogene ponparvovec (BBM-H901)[14,37]
Longest follow-up	5 y (pivotal); 5 y (phase 2b)[29,48]	~2 y (BENEGENE-2); 6 y (phase 1/2a)[53]	~4.5 y (pilot cohort)
Pivotal trial (n dosed)	HOPE-B (54)	BENEGENE-2 (45)	Phase 1/2 (6) + phase 3 (26)
Mean FIX activity[a] (SynthASil)	36 IU/dL at 5 y	≈27 IU/dL at 15 mo	55.1 IU/dL at 52 wk
Post-treatment ABR (all bleeds)	1.52 (mo 7–60)	1.28 (wk 12–mo 15)	0.6 (wk 52)
Participants with zero bleeds	26% (lead-in) → ≥67% in every 6-month period (mo 7–24)	29% (lead-in) → 64% (wk 12–mo 15)	81% (21/26) at wk 52; no individual lead-in
Anti-AAV NAb eligibility in the pivotal trial	No pre-specified threshold; efficacy preserved to 1:678 (no expression at 1:3,212)[34]	Must be negative for anti-AAVRh74var NAb	Low / absent (NAb ≤1:4; binding ≤1:200)
Immunomodulation	Reactive corticosteroids	Reactive corticosteroids	Prophylactic corticosteroids
Corticosteroid use	9/54 (17%)	28/45 (62%)	All (prophylactic); +3/26 (12%) reactive
Transaminitis (ALT rise)	10/54 (19%)	29/45 (64%)[b]	2/6 (33%, phase 1/2); 7/26 (27%, phase 3)
FIX inhibitors	None	None	None
Malignancies	3 over 5 y; all vector-unrelated	None reported	None reported
Regulatory status	FDA 2022; EMA 2023	FDA / Canada / EU 2024; withdrawn 2025[54]	NMPA China 2025; Macao 2026

[a] Mean FIX activity measured by the one-stage SynthASil assay in every case, so the values are comparable by reagent, although the timepoints, populations and

doses differ; the full standardized comparison, including the values converted from Actin FSL, is given in Table 3. b Transaminase elevation, defined as at least 1.5 times the baseline value, reported for the 45 participants dosed in BENEGENE-2; the corresponding figures for the other two products follow each trial's own definition and are not strictly comparable. AAV, adeno-associated virus; ABR, annualized bleeding rate; AE, adverse event; ALT, alanine aminotransferase; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; FIX, factor IX; mo, months; NAb, neutralizing antibody; NMPA, National Medical Products Administration; wk, weeks; y, years.

Table 3. FIX activity of the three licensed FIX-Padua products standardized to the one-stage SynthASil assay

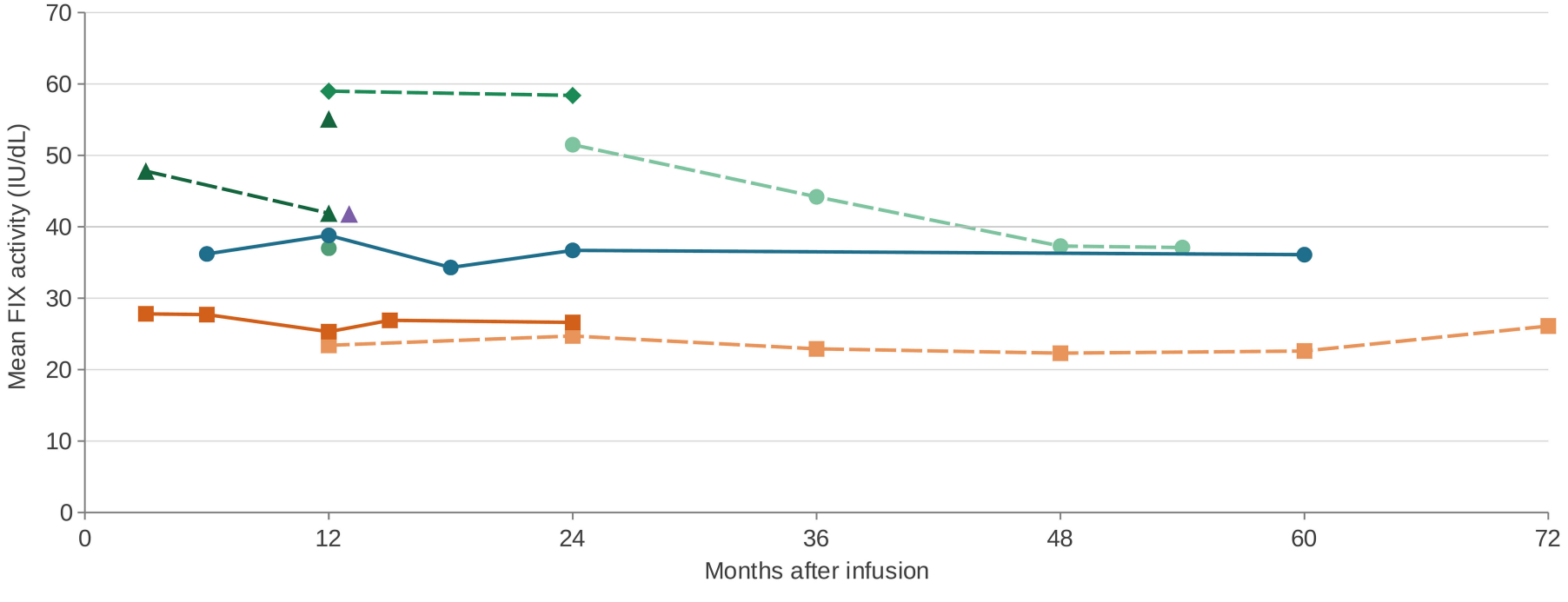
Product	Study (n dosed)	Timepoint	FIX activity as reported (IU/dL)	Standardized value (IU/dL, SynthASil)
Dalnacogene ponparvovec	Phase 3 (26)[14]	52 wk	55.1, mean (SynthASil); 41.9, mean (Actin FSL)	55.1
Dalnacogene ponparvovec	Phase 1 adolescents (11)[57]	52 wk	41.8, mean (SynthASil)	41.8
Dalnacogene ponparvovec	Phase 1/2 (6)[14]	52 wk	59, mean (Actin FSL)	≈77[a]
Dalnacogene ponparvovec	Phase 1/2 (6)[14]	104 wk	46, median; 58.4, mean (Actin FSL)	≈60 (median); ≈76 (mean)[a]
Dalnacogene ponparvovec	Pilot IIT (10)[37]	1 y	≈37, mean (Actin FSL)	≈48[a]
Etranacogene dezaparvovec	HOPE-B (54)[40]	mo 7–18	37, mean (SynthASil)	37
Etranacogene dezaparvovec	HOPE-B (54)[48]	5 y	36, mean (SynthASil)	36
Fidanacogene elaparvovec	BENEGENE-2 (45)[13]	15 mo	26.9, mean (SynthASil)	26.9
Fidanacogene elaparvovec	BENEGENE-2 (45)[13]	24 mo	26.6, mean (SynthASil)	26.6

[a] Estimated SynthASil equivalent, obtained by multiplying the published Actin FSL value by 1.3 (Methods);[12,14] shown for cross-trial orientation and not interchangeable with a measured SynthASil result. All other values were measured with SynthASil. FIX, factor IX; IIT, investigator-initiated trial; mo, months; wk, weeks; y, years.

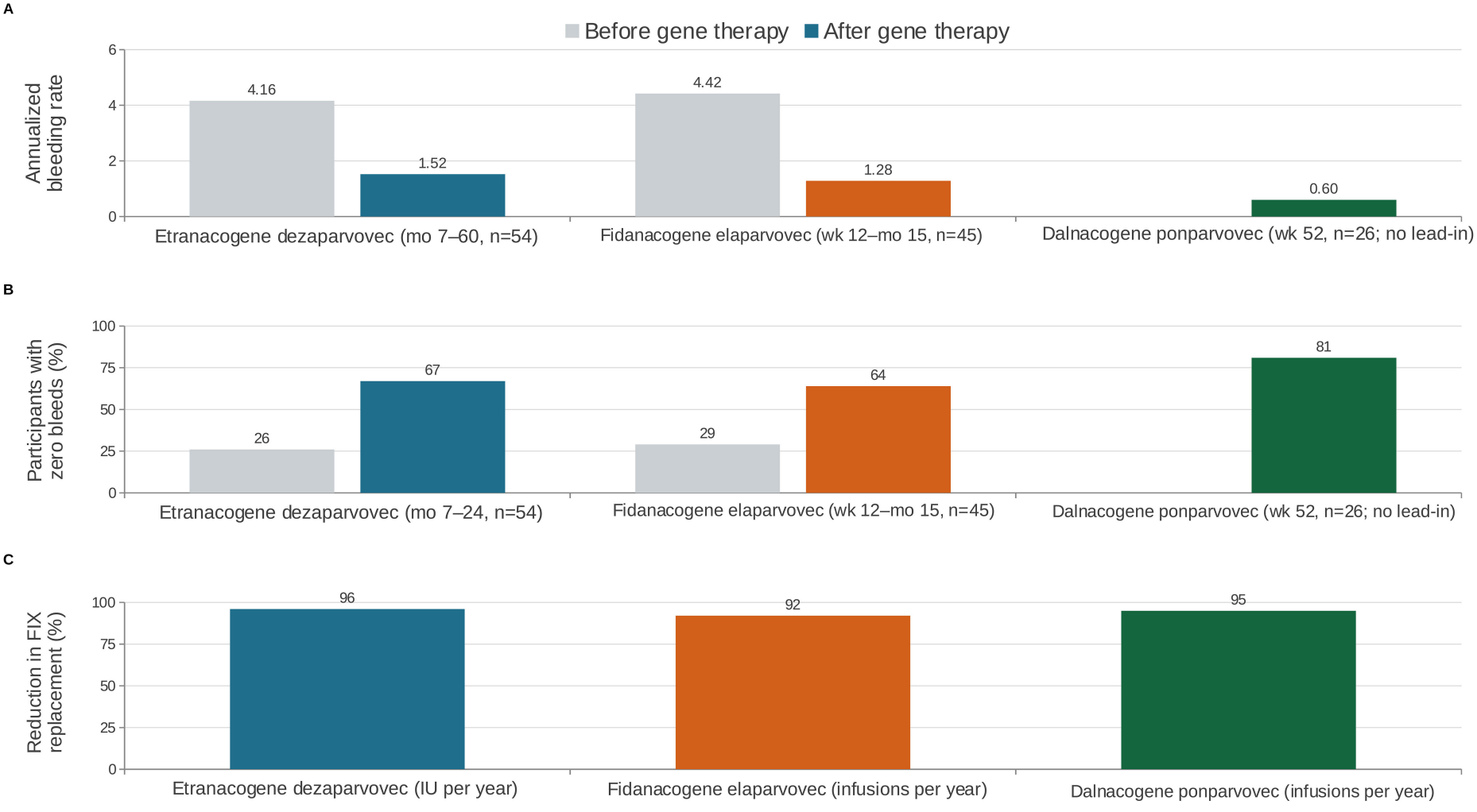
Figure 1. Mean factor IX activity after gene therapy. Values over time for etranacogene dezaparvovec (HOPE-B, n=54),[40,48,49] fidanacogene elaparvovec (BENEGENE-2, n=45,[13] and the phase 1/2a cohort followed to six years, n=15 falling to 11[52,53]) and dalnacogene ponparvovec (phase 3, n=26; phase 1/2, n=6; long-term follow-up of the pilot and phase 1/2 cohorts, n=15 at month 24, 10 at month 36 and 3 at months 48 and 54;[14] the pilot investigator-initiated trial, n=10;[37] and a phase 1 trial in adolescents, n=11[57]). All plotted values are means; for the fidanacogene phase 1/2a cohort, means of participant geometric means. Solid lines denote SynthASil values and dashed lines Actin FSL values, which read substantially lower (Methods); both phase 3 week-52 values are plotted. The HOPE-B values at months 6, 12 and 18 are least-squares mean increases from a baseline of 2 IU/dL or less and so understate the absolute mean; those at month 24 and year 5 are absolute means. The dalnacogene ponparvovec cohorts come from separate studies and are not a single trajectory, and the adolescent cohort is plotted at month 13 rather than month 12 to avoid overlap. The grey line marks 40 IU/dL, the upper limit of the mild range. FIX, factor IX; IIT, investigator-initiated trial.

Figure 2. Clinical outcomes after a single infusion of gene therapy. (A) Annualized bleeding rate for all bleeds, over months 7–60 for etranacogene dezaparvovec,[48] week 12 to month 15 for fidanacogene elaparvovec[13] and week 52 for dalnacogene ponparvovec.[14] Reported 95% confidence intervals: fidanacogene elaparvovec 1.80–7.05 before and 0.57–1.98 after gene therapy; dalnacogene ponparvovec 0.18–1.99 after. The HOPE-B final analysis reports no interval around the individual rates but gives a rate ratio for months 7–60 versus lead-in of 0.37 (95% CI, 0.18 to 0.76), a reduction of 63% (95% CI, 24 to 82).[48] (B) Proportion of participants with zero bleeds, over months 7–24 for etranacogene dezaparvovec[40,48] and over the same intervals as in (A) for the other two products. No within-patient lead-in was recorded in the dalnacogene ponparvovec phase 3 trial, so no pre-treatment value is shown for that product in (A) or (B); its trial compared the post-treatment rate with an assumed background rate of 5.0 for conventional prophylaxis in China. (C) Reduction in factor IX replacement, reported as IU per year for etranacogene dezaparvovec and as infusions per year for the other two products, so the

percentages are not interchangeable. Bar colours identify the products as in Figure 1. FIX, factor IX.



Etranacogene dezaparvovec (HOPE-B, n=54), SynthASil[40,48,49]
Fidanacogene elaparvovec (BENEGENE-2, n=45), SynthASil[13]
Fidanacogene elaparvovec (phase 1/2a, n=15→11), Actin FSL[52,53]
Dalnacogene ponparvovec (phase 3, n=26), SynthASil[14]
Dalnacogene ponparvovec (phase 3, n=26), Actin FSL[14]
Dalnacogene ponparvovec (phase 1/2, n=6), Actin FSL[14]
Dalnacogene ponparvovec (pilot IIT, n=10), Actin FSL[37]
Dalnacogene ponparvovec (pilot/phase 1/2, n=15→3), Actin FSL[14]
Dalnacogene ponparvovec (adolescents, n=11), SynthASil[57]


A
Before gene therapy
After gene therapy
Annualized bleeding rate
6
4
2
0
4.16
1.52
4.42
1.28
0.60
Etranacogene dezaparvovec (mo 7–60, n=54)
Fidanacogene elaparvovec (wk 12–mo 15, n=45)
Dalnacogene ponparvovec (wk 52, n=26; no lead-in)
B
Participants with zero bleeds (%)
100
75
50
25
0
26
67
29
64
81
Etranacogene dezaparvovec (mo 7–24, n=54)
Fidanacogene elaparvovec (wk 12–mo 15, n=45)
Dalnacogene ponparvovec (wk 52, n=26; no lead-in)
C
Reduction in FIX replacement (%)
100
75
50
25
0
96
92
95
Etranacogene dezaparvovec (IU per year)
Fidanacogene elaparvovec (infusions per year)
Dalnacogene ponparvovec (infusions per year)