Key Developments in Novel Therapies for Bleeding Disorders

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Canadian Hemophilia Society
Help Stop the Bleeding

IRISH HAEMOPHILIA SOCIETY
Cumann Haemofile Na hEireann

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Introduction

Key Developments in Novel Therapies for Bleeding Disorders is intended for a general audience—people with bleeding disorders and their families as well as health care providers—who would like a simple and concise summary of the most recent key developments in coagulation therapies to treat inherited bleeding disorders. The publication reports on clinical trial results and post-commercialization research in treatments for hemophilia A and B, von Willebrand disease, rare factor deficiencies and platelet function disorders.

The summaries in this issue are based on manuscripts published in medical journals and research abstracts presented at conferences since December 2025. These include the American Society of Hematology (ASH) Congress in December 2025 and the European Association of Haemophilia and Allied Disorders (EAHAD) Congress in February 2026.

The subjects covered were selected by the author and reviewer. The information is not intended to be comprehensive, nor to guide clinical practice. Readers are invited to consult the original publications to learn more. Links are provided.

Key Developments in Novel Therapies for Bleeding Disorders is published twice a year. The publication is a collaboration between the Canadian Hemophilia Society and the Irish Haemophilia Society.

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Factor VIII Concentrates

Efanesoctocog alfa

Susen et all reported at ASH on the Phase 3 XTEND-ed long-term extension study in adults, adolescents and children with severe hemophilia A treated with **efanesoctocog alfa** (Altuviiio, Altuvoct). The median treatment duration in 146 adults and adolescents was 166 weeks. No FVIII inhibitors were observed. The mean annual bleeding rate (ABR) was 0.70, 0.62 and 0.45 in Years 1, 2 and 3 respectively. 65%, 68% and 78% of patients reported zero bleeds in those three years. 94% of treated bleeds resolved with one infusion. No treatment-related serious adverse reactions were reported.

Among 71 children (35 aged less than 6 years, 36 aged 6-12 years), the median treatment duration was 116 weeks. No FVIII inhibitors were observed. The mean ABR was 0.68 and 0.49 in Years 1 and 2 respectively. 64% and 66% of patients reported zero bleeds in those two years. 91% of treated bleeds resolved with one infusion. No treatment-related serious adverse reactions were reported.

Researchers concluded that results from up to 4 years of the XTEND-ed study demonstrate that once-weekly efanesoctocog alfa continues to be well tolerated, providing highly effective bleed protection with no inhibitor development in adults, adolescents, and children with severe hemophilia A.

https://ashpublications.org/blood/article/146/Supplement%201/539/552327/Clinical-outcomes-up-to-4-years-of-once-weekly

Astermark et al reported in a poster at EAHAD on physical activity and efficacy in patients with severe hemophilia A on **efanesoctocog alfa** (the FREEDOM study). Patients were monitored using the International Physical Activity Questionnaire (IPAQ) and a wearable activity tracker. In total, 93 patients were enrolled. Mean physical activity levels were stable from baseline to 12 months. Overall, 15 patients reported 27 treated bleeds; 84% reported zero bleeds in the 12-month period. The researchers concluded that pre-study activity levels were high and remained so over the study period. Efanesoctocog alfa was effective in preventing bleeds despite high physical activity levels.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70195, page 56

Gene Therapy

Etranacogene dezaparvovec (Hemgenix)

The final analysis of the study of **etranacogene dezaparvovec** (Hemgenix), gene therapy for HB, with 5-year results, was published in the New England Journal of medicine (NEJM) in December 2025 by Pipe et al. Results included:

1. Fifty (50) of the 54 patients enrolled completed 60 months of follow-up. One person withdrew efficacy consent following low expression of factor IX (FIX). A second had a liver transplant and efficacy data ceased to be collected. Two people died of causes unrelated to the drug.
2. Only 3 of the remaining 50 subjects require continuous FIX prophylaxis (all previously reported). The remaining 47 subjects do not require prophylaxis. No one resumed FIX prophylaxis during Years 4 and 5.
3. The mean FIX activity level remained stable and greater than 36% during Years 1–5 post-gene therapy. Year 1: 41.5%; Year 2: 36.7%; Year 3: 38.6%; Year 4: 37.4%; Year 5: 36.1%.
4. The results for the 54 patients were as follows: Missing data (see point 1): 4 people; lack of efficacy: 2 people; 5-12% FIX: 5 people; 12-40% FIX: 26 people; 40-100% FIX: 17 people.
5. Similar outcomes were observed between AAV5 NAb-positive and NAb-negative individuals.
6. The annual bleeding rates for all bleeds in all 54 patients were: Year 1: 1.33; Year 2: 0.91; Year 3: 0.83; Year 4: 0.40; Year 5: 0.40. Most of these bleeds were in the 3 patients who returned to

prophylaxis.
7. Mean annual consumption of FIX for the 54 people was as follows: lead-in period: 257,339 IUs; Year 1: 10,532 IUs; Year 2: 8,777 IUs; Year 3: 10,218 IUs; Year 4: 9,421 IUs; Year 5: 10,900 IUs.

Researchers concluded that after a single infusion of etranacogene dezaparvovec, patients sustained clinical benefit and durable endogenous factor IX expression over a 5-year period, with levels in the mild hemophilia or no hemophilia range in more than 90% of the participants. The increased factor IX expression was associated with reductions in annualized bleeding rates and exogenous factor IX consumption. In addition, after treatment with etranacogene dezaparvovec, no evidence of oncogenicity, of long-term toxic effects on the liver, or of any substantial toxic effects, was observed after the first 6 months.

https://www.nejm.org/doi/full/10.1056/NEJMoa2514332

CSL220 (formerly AMT-060)

Miesbach et al presented a poster at EAHAD showing stable FIX expression 9 years after administration of hemophilia B gene therapy **CSL220 (formerly AMT-060)**, with the wild-type FIX gene. This was the precursor to etranacogene dezaparvovec (Hemgenix) which uses the Padua FIX gene mutation.

Nine of 10 patients from the 2 cohorts of 5 enrolled in the extension study. Median FIX activity at Year 9 was 5.0 in cohort 1 and 5.7 in cohort 2. The mean annual spontaneous bleeding rate was 2.3 in cohort 1 and 0.3 in cohort 2. No new safety events were reported in Year 9 and no patient returned to prophylaxis.

Researchers concluded that the 9-year follow-up provides evidence for the durability and safety of this AAV5-based gene therapy and that the findings are predictive of the effectiveness of etranacogene dezaparvovec.

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Valoctogogene roxaparvovec (Roctavian)

In an oral presentation at EAHAD, Klamroth et al presented 5-year data on ALT elevations after gene therapy for hemophilia A with valoctogogene roxaparvovec (Roctavian). At baseline, 15% and 31% of the 124 participants had a prior history of hepatitis B and hepatitis C infection respectively. In Year 1, 105/134 (78%) of the participants had raised ALT levels and received glucocorticoids. The numbers decreased in subsequent years: 39/134 (29%) in Year 2; 20/130 (15%) in Year 3; 21/131 (16%) in Year 4; and 23/129 (18%) in Year 5. After Year 2, no elevations were greater than 5X the upper limit of normal. Most elevations were transient. The data showed that most elevations were transient and mild, peaking in Year 1, then decreasing and stabilizing.

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FVIII Mimetics

Mim8 (Denecimig)

In an oral presentation at ASH, Lentz et al reported on efficacy and safety outcomes in adults and adolescents with hemophilia A receiving **Mim8** prophylaxis in the phase 3 FRONTIER2 study. For the first 26 weeks (main phase), the 281 participants were randomized to Mim8 once weekly (QW), Mim8 once monthly (QM) or continued on-demand treatment with clotting factor. In the final 26 weeks (extension phase), all on-demand patients were switched to Mim8 QW or QM; those on Mim8 continued either weekly or monthly. For those previously on FVIII prophylaxis, 67% and 70% of patients on QW had zero bleeds and mean ABRS of 2.32 and 1.28 in the main and extension phases respectively. On QM, 63% and 69% of patients had zero bleeds and mean ABRs of 1.79 and 1.54 in the main and extension phases respectively. Anti-Mim8 antibodies were detected in 7% of recipients with no clinical evidence of neutralizing activity. No thromboembolic events or hypersensitivity reactions were reported.

https://submit.hematology.org/program/presentation/677635

In an oral presentation at EAHAD, Kenet at al presented 52-week safety and efficacy outcomes in children with hemophilia A, aged 1-11 years, on **Mim8** prophylaxis (FRONTIER3). The 70 patients received the subcutaneous injections once per week (QW) for 26 weeks (Part 1); 32 then chose to switch to monthly injections (QM) for the final 26 weeks (Part 2). No severe transfusion-related adverse events were reported. No thromboembolic or hypersensitivity reactions occurred. Anti-Mim8 antibodies developed in 5/70 (7%), but none was neutralising. The mean ABR for treated bleeds in the QW group was 0.53 in Part 1 and 0.42 in Part 2, and 0.50 overall. For those on QM in part 2, the ABR was 0.25. No patients with HA and inhibitors reported bleeds. All 10 target joints at baseline had resolved by Week 52. All patients choose to continue to FRONTIER4, the extension study.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70195, page 16

In a poster at EAHAD, Hermans at al presented 52-week patient-reported outcomes in adolescents and adults with hemophilia A, with and without inhibitors, on **Mim8** prophylaxis (FRONTIER2).

The 281 patients received the subcutaneous injections once per week (QW) for 52 weeks, or QW for 26 weeks and once monthly (QM) for the next 26 weeks. QW and QM results were consistent. Patient-reported outcomes were measured using the Hemophilia Treatment Experience Measure (Hemo-TEM), the Pediatric Quality of Life Inventory (PedsQL) and the Hemophilia Patient Preference Questionnaire. Researchers concluded that Mim8 prophylaxis was associated with lasting improvements in treatment burden, physical function and joint pain compared to previous treatment: prophylaxis or on-demand treatment with clotting factor concentrate. Patients expressed a strong preference over previous therapies.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70195, page 58

In a poster at EAHAD, Fijnvandraat et al described caregiver-reported outcomes in children on **Mim8** prophylaxis (FRONTIER3). Caregiver-reported treatment burden and health-related QoL were assessed using the Child Hemophilia Treatment Experience Measure (Child Hemo-TEM) and the Pediatric QoL Inventory (PedsQL). Before the study, 40/70 (57%) received factor concentrate prophylaxis, 25/70 (36%) received concentrates on-demand, and 5/70 (7%) were untreated or were on immune tolerance induction (ITI). Caregiver-reported outcomes suggest that Mim8 prophylaxis has the potential to reduce treatment burden and improve physical functioning in children.

NXT007

In an oral presentation at EAHAD, Nogami et al reported on the safety, pharmacodynamics and efficacy of **NXT007**, an emicizumab-based, next-generation bispecific antibody which mimics FVIII, in patients with hemophilia A, with and without inhibitors, after switching from emicizumab.

Fourteen patients, aged 12-65 years, received NXT007 in four dose cohorts without a washout period for emicizumab. Patients in the two higher dose cohorts achieved estimated FVIII equivalence at the non-hemophilic level (above 40%). NXT007 was well tolerated with no thromboembolic events and no increases in D-dimer. One patient developed an anti-drug antibody, but continued in the study with no bleeding events. The higher dose cohorts demonstrated robust hemostatic control, zero treated bleeds and normalized thrombin generation.

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In a poster presented at EAHAD, Nakajima et al presented data on the normalization of global coagulation potential with **NXT007**. Five of the 12 patients in the phase 1/2 trial were switched from FVIII prophylaxis, the other 7 from emicizumab. Patients received a loading dose and weekly injections in 4 cohorts with ascending doses. The coagulation potential of NXT007 was assessed using thromboelastometry and thrombin generation assays. The potential increased in a dose-dependent manner. In the two highest dose cohorts, the coagulation potential was estimated to be comparable to that of healthy individuals.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70195, page 96

Re-balancing Agents

VGA039

In an oral presentation at EAHAD, Yamaguti-Hayakawa et al presented results from a phase 1/2 clinical trial of **VGA039** in patients with von Willebrand disease. VGA039 is a fully human IgG4 monoclonal antibody that inhibits Protein S anticoagulant activity and enhances thrombin generation. Six received a flat dose; the 10 others received doses based on weight. There were no serious drug-related adverse events or significant elevations in D-dimers.

Sixteen symptomatic patients with various VWD types/subtypes, aged 15-53 years, received a loading dose and 5 subsequent doses every 4 weeks. Three patients with an ABR over 12 experienced reductions between 72% and 80%. Researchers concluded that the results support dose regimen optimization to inform dose selection for a phase 3 trial.

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In a poster presented at EAHAD, Sakurai et al demonstrated that **VGA039** restores hemostasis in von Willebrand disease in an ex vivo model. In this study, whole blood treated with VGA039 was perfused on a hemostasis-on-a-chip model. While samples from VWD patients showed significantly longer bleeding times compared to healthy volunteers, treatment of the samples with VGA039 reduced ex-vivo bleeding times and normalized bleeding parameters. These reductions in bleeding times were associated with accelerated rates of platelet and fibrin deposition. Researchers concluded that this provides evidence for the correction of hemostatic deficiencies in VWD patients with VGA039.

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Marstacimab (Hympavzi)

In a late-breaking oral presentation at EAHAD, Mahlangu et al reported on the death of a person with hemophilia A and inhibitors in the marstacimab BASIS Open Label Extension (OLE) study. The day of surgery to remove a ureteral stent for kidney and urinary tract stones, under rFVIIa coverage, the patient suffered multiple cerebral infarctions. Almost two weeks later, he suffered a minor cerebral hemorrhage which worsened, leading to his death.

In separate reports, a 24-year-old patient, also on the BASIS OLE, with other risk factors for thrombosis including previously undiagnosed Factor V Leiden, a condition associated with a higher risk of thrombosis, developed deep vein thrombosis after three years on marstacimab. Two cases of thrombosis have been reported following marketing approval. The first, in a 41-year-old with hemophilia A without inhibitors, was associated with off-label (more frequent than prescribed) dosing of marstacimab combined with FVIII, and likely caused a coronary infarction. The second occurred in a 51-year-old with hemophilia B who experienced neurological symptoms, likely associated with marstacimab.

In an oral presentation at EAHAD, Mahlangu et al reported on joint health in patients with hemophilia A or B, with inhibitors, treated with **marstacimab** in the phase 3 BASIS trial.

Of 60 patients in the 6-month observational phase (OP), aged 12-75 years, 47 had severe hemophilia A and 13 had moderate-to-severe hemophilia B, and 51 went on to the active treatment phase (ATP). They were treated for one year with marstacimab: a loading dose and then once weekly. The annual bleeding rate (ABR) decreased from 15.15 in the OP to 1.1 in the ATP. At study entry, 43/60 patients had at least one target joint. This decreased from 0.6 in the OP to 0.0 at the end of the ATP. Hemophilia Joint Health Scores improved modestly. Researchers concluded that in patients with inhibitors marstacimab markedly reduced joint bleeding and the number of target joints.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70195, page 16

In a poster at EAHAD, Coppola et al reported on the immunogenicity of marstacimab, as part of the BASIS trial in people with hemophilia A or B, with inhibitors. Of the 51 patients who received marstacimab over one year, 10 developed anti-drug antibodies (ADA). Titers were low and 9/10 had resolved by end of study. Neutralizing antibodies were detected in 2/10 but were negative in both by end of study. Annualized bleeding rates for treated bleeds were comparable between ADA+ and ADA- patients. One treatment-related adverse event, a grade 3 rash, resulted in study discontinuation.

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