KEY DEVELOPMENTS IN NOVEL THERAPIES FOR BLEEDING DISORDERS

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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, marketing authorisations and post-commercialisation research in treatments for hemophilia A and B, von Willebrand disease, rare factor deficiencies and platelet function disorders, including Glanzmann Thrombasthenia.

The summaries in this issue are based on manuscripts published in medical journals and research abstracts presented at conferences since April 2026, notably the International Society of Hemostasis and Thrombosis (ISTH) Congress in July 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. ISTH abstracts can be found at isthcongress.org/abstracts.

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

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FACTOR VIII CONCENTRATES

EFANESOCTOCOG ALFA (ALTUVIIIO, ALTUVOCT)

Efanesoctocog alfa is an ultra-extended FVIII concentrate, infused intravenously, manufactured by Sanofi/Sobi.

Joint health in patients with severe haemophilia A treated with efanesoctocog alfa: 12-month interim results from the FREEDOM study (ISTH 2026, OC 43.1)

Christoph Königs et al reported on joint health in patients with severe haemophilia A treated with efanesoctocog alfa: 12-month interim results from the FREEDOM study. Joint health was assessed using the Haemophilia Joint Health Score (HJHS) and Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) in 91 patients, aged 12 and over. They concluded that efanesoctocog alfa prophylaxis was highly effective in preventing joint bleeds. Most patients had no treated joint bleeds over 12 months. Despite previous FVIII prophylaxis, approximately half of patients entered the FREEDOM study with synovial hypertrophy (SH) in one or more joints; of these, half had SH reduction or resolution after 12 months of efanesoctocog alfa.

GENE THERAPY

DALNACOGENE PONPARVOVEC (BBM-H901)

BBM-H901 is an AAV vector-based gene therapy for hemophilia B, infused intravenously just once, manufactured by Shanghai Xinzhi BioMed Co., Ltd. It is the first AAV vector-based gene therapy approved in China and the third gene therapy for hemophilia B approved worldwide.

Efficacy and safety of dalnacogene ponparvovec (BBM-H901) gene therapy in adults with moderate to severe hemophilia B: Pooled analysis of long-term follow-up data from phase I/II/III trials in China (ISTH 2026, OC 21.2)

Feng Xue et al reported on the efficacy and safety of dalnacogene ponparvovec (BBM-H901) gene therapy in adults with moderate to severe hemophilia B with pooled data from phases 1/2/3 for 32 patients from eight sites. It uses the Padua FIX mutation. Prophylactic oral prednisone was given at a dose of 1 mg/kg/d and tapered off in around 8-10 weeks. FIX activity, annual bleeding rate (ABR) and adverse events (AEs) were measured regularly. All participants completed 2-year follow-up. The mean FIX activity tested by the one stage assay with (HemosIL SynthASil) reagents was 61.3%. At week 104, 5 participants (16.7%) had endogenous FIX in the range of 5-40% and 23 participants (76.7%) over 40%. The ABR for all bleeding episodes decreased to 0.48 during the first year after treatment. The proportion of participants with zero treated bleeding events was 84.4% (27/32) during the 2-year follow-up. The mean target joints number decreased from 1.1 to 0 after infusion. No drug related serious adverse events, inhibitors, thrombotic events or tumors were observed during the follow-up. They concluded that dalnacogene ponparvovec can provide HB patients with continuous and stable FIX expression with no new safety concerns throughout long-term follow up.

REGV131-LNP1265, FACTOR IX GENE INSERTION THERAPY IN PEDIATRIC, ADOLESCENT AND ADULT PARTICIPANTS WITH HEMOPHILIA B (NCT06379789)

Regeneron is enrolling up to 130 people in the clinical trial program for its experimental CRISPR/Cas9-based gene insertion therapy. Eligibility criteria include confirmed diagnosis of severe or moderately severe hemophilia B with medical history of FIX functional activity of ≤2% or documented genotype known to produce severe hemophilia B, currently taking FIX prophylaxis, previous experience with FIX therapy, and participation in the lead-in period of this interventional study. Phase 1/2 enrollment has begun.

BE-101

In June 2026, Be Biopharma ended its phase 1/2 BeCoMe-9 study of BE-101, an investigational cell therapy for hemophilia B. The trial was reportedly discontinued as a strategic business decision and was not linked to any safety concern. The study had enrolled five of an anticipated 24 patients before it was halted. The therapy used a patient's own cells, modified outside the body to produce FIX, with the potential to be re-dosed if needed.

FVIII MIMETICS

EMICIZUMAB (HEMLIBRA)

Emicizumab is a humanized bispecific antibody that mimics FVIII in the coagulation cacade, designed as routine prophylaxis by Roche-Chugai to treat hemophilia A. It is administered subcutaneously weekly (QW), every two weeks (Q2W) or every four weeks (Q4W).

Comparative effectiveness of standard and lower dose emicizumab prophylaxis across age groups in severe hemophilia A in India (ISTH 2026, OC 71.2)

Rucha Patil et al reported on the comparative effectiveness of standard dose and two lower doses of emicizumab prophylaxis in severe hemophilia A in India. Using a structured form, 20 centres across India reported bleeding outcomes in 703 patients of all ages. Thirty percent (30%) had inhibitors. The Standard Dose (SD) cohort (n=268) received a loading dose of 3 mg/kg/wk x 4 weeks, followed by 6 mg/kg/Q4W; the lower dose (LD1) cohort (n=271) received 3 mg/kg/Q4W; the Lowest Dose (LD2) cohort (n=164) received 1.5 mg/kg/Q4W. At baseline, all patients had high bleeding burden. This was reduced profoundly by >95% at all doses across all age groups. ABRs decreased markedly, from 22.0, 31.2 and 42.7 pre-treatment to 0.6, 0.4 and 0.7 post-treatment in the SD, LD1, and LD2 groups, in the three dosing regimens respectively. The zero-bleed rate at follow-up of 1.7 years was high across all dosing regimens: adults 79.6% (SD), 78.6% (LD1), 74.4% (LD2); older children 81.4%, 82.8%, 73.6%; young children 88.1%, 88.6%, 82.4%. Joint health, functional outcomes, and QoL improved significantly across all regimens. The researchers concluded that in this large real-world cohort of people with hemophilia A, standard and lower doses of emicizumab showed excellent hemostatic efficacy with no significant differences between regimens.

DENECIMIG (MIM8)

Denecimig is a humanized bispecific antibody that mimics FVIII in the coagulation cacade, designed as routine prophylaxis by Novo Nordisk. It is administered subcutaneously weekly (QW), every two weeks (Q2W) or monthly (QM).

Mim8 (denecimig) prophylaxis in adults and adolescents with haemophilia A with or without inhibitors (ISTH 2026, OC 02.4)

Jerzy Windyga et al reported interim results from the FRONTIER4 long-term safety and efficacy extension study of denecimig in 365 participants aged 12 years and over. 87% had severe hemophilia A; 11% had FVIII inhibitors (HAwI). Over a mean treatment analysis period of 0.57 years, no thromboembolic events were reported. Of 6138 injections, 1.8% resulted in injection site reactions (ISRs), including 0.4% associated with pain/burning. All ISRs were mild in severity and transient. Anti-denecimig antibody incidence was 4.7% with no clinical evidence of neutralising effect. ABRs for people with HA and HAwI were 0.88 (0.71-1.08) and 0.15 (0.05-0.45), respectively, across QW, Q2W and QM dosing frequencies. The proportions of participants with zero treated-bleed rates were 70.4%, 80.8% and 70.9%, respectively. Researchers concluded that interim analysis from FRONTIER4 supports the long-term safety and efficacy of denecimig prophylaxis in adults and adolescents with consistently low ABRs across flexible dosing frequencies and inhibitor status.

Mim8 (denecimig) prophylaxis in children with haemophilia A with or without inhibitors: Interim safety and efficacy results from the FRONTIER4 long-term extension study (ISTH 2026, OC 02.5)

Manuel Carcao et al reported on interim safety and efficacy results from the FRONTIER4 long-term extension study in children with or without inhibitors receiving Mim8 (denecimig) prophylaxis, previously enrolled in the FRONTIER3 study. Of 61 male children, aged 1 to 11 years, 90% had severe hemophilia A, and 23% had FVIII inhibitors. There were no thromboembolic events or hypersensitivity reactions. Of 839 injections, 2.0% resulted in injection site reactions (ISRs), including 0.8% associated with pain and/or burning. All ISRs were mild in severity and transient. There was no clinical evidence of neutralising anti-denecimig antibodies.Estimated mean annualised bleed rates (ABRs) were low across dosing frequencies: 0.50 and 0.37 for QW and QM, respectively, while no treated bleeds were observed for Q2W. For QW, Q2W and QM, respectively, 85.2%, 100.0% and 88.5% of children had zero treated bleeds during the 0.37-year mean observation period. Estimated mean ABRs in HA and HAwI participants were 0.42 and 0.20, respectively. The researchers concluded that these interim results align with FRONTIER3 data, further supporting the safety and efficacy of denecimig.

Denecimig (mim8) restores thrombin generation into the normal range in people with haemophilia A (ISTH 2026, PB 2069)

Guy Young et al reported on their in vitro analyses measuring the level of thrombin generation achieved with denecimig. Previous studies had found a 15-fold increase in potency for thrombin generation in denecimig compared to emicizumab. Samples from 185 and 61 patients with hemophilia A from the FRONTIER2 and FRONTIER5 studies respectively, 12 years and over with and without inhibitors, were analysed using a thrombin generation assay. Thrombin peak height with denecimig prophylaxis in FRONTIER5 showed a sustained increase into the normal reference range, consistent with FRONTIER2 findings. Mean thrombin peak height with denecimig prophylaxis during FRONTIER5 was comparable to 40% FVIII activity. Researchers concluded that denecimig increased thrombin generation into the low normal reference range. These findings support denecimig as an ultra-potent activated FVIII mimetic, confirmed by efficacy outcomes demonstrated in p 3 clinical studies in people with HA, independent of inhibitor status.

NXT007

NXT007 is a next-generation investigational bispecific antibody that mimics FVIII in the coagulation cascade, being investigated by Roche-Chugai as a prophylactic (preventive) treatment option for people with haemophilia A. It is administered subcutaneously every four weeks (Q4W).

NXT007 prophylaxis in people with hemophilia A with or without factor VIII inhibitors: Combined analysis of two phase I/II multiple ascending-dose studies (ISTH 2026, OC 02.2)

Maria Elisa Mancuso et al reported on two phase 1/2 multiple ascending-dose studies of NXT-007, a next-generation bispecific antibody based on emicizumab that mimics activated factor FVIII function in people with hemophilia A. Participants were aged 12-64 and were emicizumab-naïve. After loading doses, the three cohorts received sub-cutaneous doses of 0.28, 0.70, and 1.08mg/kg, respectively, every 4 weeks. Overall, 42 people received NXT-007; 95% had severe HA and one person had a FVIII inhibitor. NXT007 had favorable safety outcomes across all doses. ABRs for treated bleeds were 0.3 in the maintenance period. 36/42 (85.7%) participants had zero treated bleeds. NXT007 plasma concentrations increased dose-dependently. Overall, 34/42 (81.0%) participants developed anti-drug antibodies (ADAs); one had an ADA impacting pharmacokinetics; none impacted safety or cross-reacted with emicizumab. Researchers concluded that NXT007 had favorable safety outcomes, with low treated ABRs and that these data support progression to phase 3 trials.

Major surgeries in people with hemophilia A under NXT007 prophylaxis: Experience from NXTAGE phase I/II (ISTH 2026, OC.02.3)

Keiji Nogami et al reported on the first case series of surgeries in people treated with NXT-007. The three people in the NXTAGE study were receiving NXT007 at 0.7 and 1.08 mg/kg once every four weeks (Q4W). Patient 1, a 56-year-old non-inhibitor patient underwent laparoscopic cholecystectomy for polyps in the gallbladder. Single doses of 1,000 IU (16.7 IU/kg) extended-half-life FVIII were administered preoperatively on surgery day and the following day, respectively. Patient 2, a 52-year-old non-inhibitor patient underwent total elbow arthroplasty for ulnar nerve disorder. A single dose of 1,000 IU (12.7 IU/kg) standard-half-life FVIII was administered preoperatively on surgery day. Patient 3, a 24-year-old inhibitor patient with worsening of hemophilic arthropathy of the right ankle, underwent arthroscopic synovectomy. Perioperatively, oral tranexamic acid was used but not coagulation factor products. In all three cases, no surgery-related bleeds and no thrombotic events occurred after these surgeries. The researchers concluded that in patients receiving NXT007 at doses ≥0.7 mg/kg Q4W in NXTAGE, major surgeries including orthopedic surgeries with high bleeding risk were safely performed under perioperative management with no or minimal use of coagulation factor products. These findings support hemostatic normalization with NXT007, although further accumulation of surgical cases is warranted.

INNO8

Inno8 is a bispecific heavy-chain-only antibody fragment that mimics activated factor VIII and is being developed by Novo Nordisk as a once-daily oral prophylaxis for hemophilia A.

Inno8 is the first orally administered factor VIII mimetic to show favourable safety, pharmacokinetic, and pharmacodynamic properties in healthy male participants (ISTH 2026, LB 02.3)

Linda Ingemann et al reported on VOYAGER1. To enable oral bioavailability, Inno8 is formulated as a tablet with salcaprozate sodium (SNAC), an absorption enhancer that facilitates gastric epithelial uptake. VOYAGER1 (NCT06649630) was a randomized, placebo-controlled, first-in-human phase 1 study with single ascending dose and multiple ascending dose parts in healthy male participants. PK was dose proportional. Dose-dependent changes in aPTT and thrombin peak height were observed across the dose range for intravenous and oral administration of Inno8. The researchers concluded that Inno8 was safe and well tolerated across all tested intravenous and oral dose levels. The dose-proportional pharmacokinetic and pharmacodynamic effects support further clinical development of Inno8 as an oral prophylaxis for hemophilia A.

REBALANCING AGENTS

VGA039 (LATARCIBART)

Latarcibart is a fully human IgG4 monoclonal antibody that targets Protein S with a dual action on tissue factor pathway inhibitor alpha and activated Protein C pathways, promoting platelet deposition and enhancing fibrin, being developed by Incyte.

Subcutaneous four-week dosing of the novel protein S antibody VGA039 demonstrates safety and clinically meaningful bleed reduction in patients with von Willebrand disease (ISTH 2026, OC 32.3)

Alison Wheeler et al presented results from a phase 1/2 study of VGA039 (Latarcibart). Initial data demonstrated safety and pharmacodynamic activity with reduction in bleeding events. The multi-dose study evaluated the safety, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous (SC) VGA039 prophylaxis in patients in von Willebrand disease. Participants received six doses of SC VGA039 over 120 days, with up to 42-day follow-up and optional participation in an open-label extension study. A total of 16 participants, aged 15-53 years with all VWD types, received a single SC loading dose on Day 1, followed by SC maintenance doses every 4 weeks starting on Day 8. There were no serious drug-related adverse events or clinically significant D-dimer elevations. VGA039 achieved plasma concentrations in the therapeutic range. Eight participants who completed the treatment period, including two participants switching from IV prophylaxis, experienced annualised bleeding rate (ABR) reductions of 41-100% (median: 81%). Researchers concluded in this heterogeneous VWD study population that SC Q4W VGA039 was well tolerated and efficacious, supported by pharmacokinetic data and meaningfully reduced bleeding in participants with high historical ABRs. These findings support continued clinical development in the ongoing phase 3 VWD trial.

Pharmacokinetic and pharmacodynamic characterization of VGA039, a protein S-targeting monoclonal antibody, supports subcutaneous every-4-week dosing for routine prophylaxis in phase 3 VWD trial (ISTH 2026, PB2083)

In another study on VGA039, Christopher DelNagro et al analysed pharmacodynamics in healthy volunteers and people with VWD and concluded that VGA039 exhibits a favorable PK profile that supports SC Q4W dosing. These PK/PD findings establish and confirm the population PK model used for dose and regimen selection for VGA039 as a routine prophylactic in the phase 3 trial.

FITUSIRAN (QFITLIA)

Fitusiran is a first-in-class RNA interference (RNAi) therapy that lowers antithrombin (AT) to rebalance hemostasis in people with hemophilia A or B, with or without inhibitors. It is manufactured by Sanofi/Sobi as a subcutaneous prophylactic treatment. Dose is adjusted based on antithrombin levels. It was approved by the U.S. FDA in 2025 as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A or hemophilia B, with or without factor VIII or IX inhibitors.

Safety and efficacy of the fitusiran antithrombin-based dose regimen people with hemophilia A and B by age group (ISTH 2026, PB2126)

Guy Young et al presented data on safety and efficacy of fitusiran (Qfitlia) with an

antithrombin-based dose regimen by age group in hemophilia A and B. The AT-based dose regimen in the ATLAS-OLE extension study targeted AT levels of 15-35%. Overall, 286 participants (60 adolescents aged 12–17 years, 233 adults aged 18–64 years, and 3 elderly adults over 65 years), were included in the analysis. The proportion of participants with any treatment-emergent adverse events (TEAEs) and serious adverse events were similar, irrespective of age. Notably, there were no treatment discontinuations due to TEAEs in the adolescent population. One of 60 adolescents, three of 266 adults and none of the three elderly participants experienced a thrombotic event; no transaminase elevations greater than 3x the upper limit of normal were reported in adolescents. Efficacy analyses were based on 213 participants (39 adolescents, 171 adults, and 3 elderly adults). Observed median ABRs were 3.7 (0.0, 11.2) in the adolescent population and 3.7 (0.0, 7.5) in both the adult and overall populations. A total of 40% of adolescents had no bleeds compared to 28.9% of adults. Researchers concluded that a similar safety profile and clinically meaningful bleed control were observed in adolescents aged 12–17 years and in adults. These data indicate the suitability of fitusiran prophylaxis for bleeding control for all PwH, irrespective of age.

MARSTACIMAB (HYMPAVZI)

Marstacimab is an anti-tissue factor pathway inhibitor (TFPI), manufactured by Pfizer as a subcutaneous prophylactic treatment for hemophilia A and B. It is injected weekly.

In May, the European Commission (EC) expanded indications for marstacimab (Hympavzi) to include routine prophylaxis in patients with severe hemophilia A or B, with or without inhibitors, aged 12 years and older, weighing at least 35 kg.

In June, the U.S. Food and Drug Administration (FDA) also expanded indications for marstacimab (Hympavzi), to include routine prophylaxis in patients aged 6 years and older with hemophilia A or hemophilia B, regardless of inhibitor status.

Marstacimab prophylaxis in pediatric participants with hemophilia A or B with or without inhibitors (ISTH 2026, LB 02.1)

Gil Kenet et al reported interim results from the phase 3 BASIS KIDS trial for marstacimab (Hympavzi). Participants—25 with inhibitors, 67 without inhibitors—received a subcutaneous marstacimab loading dose followed by once-weekly dosing for 12 months. Of these, 54 completed the study, 3 discontinued and 35 were ongoing. In the 54 who completed, ABRs were 1.44 compared to 18.92 with previous on-demand treatment for inhibitor patients, and 1.84 vs. 3.55 for those on previous regular prophylaxis. There were no deaths, thrombotic events, or permanent discontinuations from treatment due to adverse events. Researchers concluded that interim results suggest marstacimab is effective and safe for pediatric patients with HA or HB, with or without inhibitors, aligning with previous findings in adolescents and adults.

HMB-002

HMB-002 is a subcutaneously administered monovalent antibody designed for prophylaxis in patients with various VWD subtypes, in development by Hemab. By binding to circulating von Willebrand factor (VWF), HMB-002 elevates both VWF and FVIII levels.

First-in-human investigation of HMB-002: A subcutaneous antibody for prophylactic management of V on Willebrand disease (ISTH 2026, OC 12.5)

Priyanka Raheja et al presented interim results from the first-in-human study of HMB-002 in VWD. The study aim was to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following a single subcutaneous dose of HMB-002. A greater than 150% change in VWF and FVIII was achieved and maintained for at least 8-10 days. Restoration of thrombin generation to the normal range and shortening of APTT were observed. HMB-002 demonstrated a favorable safety profile with no reported related treatment-emergent adverse events, injection site or hypersensitivity reactions, changes in D-dimer levels or inflammatory markers, or detectable antidrug antibodies at any timepoint. HMB-002 was well-tolerated and produced sustained dose-dependent increases in PK, and PD (VWF and FVIII), supporting proof of mechanism and the potential for infrequent subcutaneous dosing. Researchers concluded that these interim results support continued dose escalation to further evaluate PD magnitude and durability.

SUTACIMIG (FORMERLY HMB-001)

Sutacimig is a novel bispecific antibody designed to bind endogenous factor VIIa (FVIIa) and localize it to activated platelets via TLT-1, thereby augmenting thrombin generation at sites of vascular injury. It is developed by Hemab.

Sutacimig prophylaxis in Glanzmann Thrombasthenia: Results from a phase 2 long-term extension (ISTH 2026, OC 57.3)

Quentin Van Thillo et al reported on this study to evaluate sutacimig as prophylactic therapy for Glanzmann Thrombasthenia (GT). Thirty-four adults received sutacimig for 12 weeks in four dosing cohorts; 28 continued in the extension study. Adverse events were predominantly mild to moderate. Three treatment-related thromboembolic events occurred (all grade 2, with multiple concurrent risk factors, managed with anticoagulation). Three participants underwent procedures, 2 invasive surgeries and 1 dental procedure, all with successful hemostatic outcomes requiring minimal to no intervention. The weekly dosing cohort (n=4) had 87% annualised treated bleeding rate (ATBR) reduction. Seven participants achieved 100% ATBR reduction. Researchers concluded that the safety and clinical activity results continue to support the potential of sutacimig as the first prophylactic therapeutic option for GT and will inform optimal dose selection and study design for phase 3 development.

SR604

SR604, a humanized monoclonal antibody that selectively inhibits the anticoagulant activity of activated protein C while preserving its anti-inflammatory and cytoprotective signaling. It is being developed for hemophilia A and B by Shanghai Raas.

Long-acting prophylaxis through targeted activated protein C modulation: Phase IIb results of SR604 (ISTH 2026, LB 02.2)

Renchi Yang et al presented data on the phase 2b study whose purpose was to evaluate the safety, durability, and extended-interval prophylactic efficacy of SR604 in 36 patients with hemophilia A or B. Patients received subcutaneous SR604 Q4W, Q6W or Q8W for 24 weeks with an optional 24-week extension. Results demonstrated strong prophylactic efficacy and a favorable safety profile of SR604 in hemophilia, including dosing intervals up

This publication was co-produced by Bleeding Disorders Canada and the Irish Haemophilia Society

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