EHC
Empowering the bleeding disorders community

Novel Treatment Review (NTR)

A periodic EHC Review

July 2026 - Issue

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Foreword

Welcome to the second edition for 2026 of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia, von Willebrand disease and other rare bleeding disorders.

The purpose of this newsletter is to provide up-to-date information to our broader community and particularly to EHC National Member Organisations (NMOs), and a general overview and understanding of the rapidly evolving landscape of coagulation product developments in rare bleeding disorders. The EHC encourages its NMOs to use and adapt the information contained in this review at a national level with patients and caregivers, healthcare providers and other interested stakeholders, but takes no responsibility for any changes. This newsletter provides information by specific type of disorder— haemophilia A, haemophilia B, von Willebrand disease and other rare bleeding disorders—and by product class: factor replacement therapies, bypassing agents, mimetics, rebalancing therapies and gene therapy.

Note that bypassing agents and rebalancing therapies have been given their own categories separate from specific bleeding disorders as they may be of use across multiple conditions. This publication covers developments in coagulation products that are in clinical trials, that have recently received marketing approvals or whose indications are being expanded, but does not delve into the basic science of rare bleeding disorders and their treatments. To obtain this type of information, we would suggest consulting the EHCucate app (available on iOS and Google Play), which provides basic scientific concepts on rare bleeding disorders and the mechanisms of action of their treatments, and the World Federation of Hemophilia education and e-learning section : (https://wfh.org/education-and-elearning/)

In this edition, we primarily cover advances presented at the EAHAD Congress held in February 2026, WFH World Congress held in April 2026, and ISTH Congress held in July 2026, as well as other industry updates and news in general.

The first section, an Update on Recent Marketing Authorisations and Indication Expansion and Early Clinical Trials, provides news announced since February 1, 2026.

The second section, Report Highlights, summarises very concisely some of the key advances since the last edition of this review in February 2026 in each of the disease areas and product classes.

The third section, Research Abstracts and Articles, reproduces publications from the medical literature. The abstracts can be found in their original versions at:

EAHAD Congress abstracts:
https://onlinelibrary.wiley.com/toc/13652516/32/S1

WFH World Congress abstracts:
https://onlinelibrary.wiley.com/toc/13652516/2026/32/S2

ISTH Congress abstracts:
https://isth.m-anage.com/programme?segment=abstracts&sort=short&view=list

In the last section, for your convenience, we include a table on all treatments covered in this newsletter, both in development and licensed, as well as other novel treatments under development. We hope this will facilitate your understanding of the changing therapeutic landscape.

Acknowledgments

The EHC wishes to thank its Novel Treatment Review (NTR) Committee, which has overseen the content and production of this newsletter. Its members include:

- Dr Paul Batty, EHC volunteer
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- Dr Robert Klamroth, EHC volunteer
- Prof Cédric Hermans, EHC volunteer

We hope that the information contained herein is useful and we are available for any questions.

Sincere regards,

Tatjana Marković, EHC President

Disclaimer

The EHC produces this publication primarily as an educational tool for its NMOs. With the continually changing therapeutic environment, the EHC aims at publishing updates twice yearly. The information contained, and the views expressed herein, constitute the collective input of the EHC NTR Committee. The EHC does not engage in medical practice and under no circumstances recommends a particular treatment for specific individuals. The EHC makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons, the EHC strongly recommends that individuals seek the advice of a medical adviser and consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this publication. The EHC does not endorse particular treatment products or manufacturers; any reference to a product name is not an endorsement by the EHC. The EHC welcomes all treatment developments that may benefit patients in the future.

Abbreviations

Ab	*Antibodies*	**DVT**	*Deep vein thrombosis*
AAV	*Adeno-associated virus*	**EAHAD**	*European Association for Haemophilia and Allied Disorders*
ABR	*Annualised bleeding rate*	**EC**	*European Commission*
ADAs	*Anti-drug antibodies*	**ECLA**	*ElectroChemiLuminiscence Assay*
AE	*Adverse events*	**ED**	*Exposure days*
AFP	*Alphafetoprotein*	**EHL**	*Extended half-life*
ALT	*Alanine transaminase*	***ELISA***	*Enzyme-linked immunoassay*
AjBR	*Annualised joint bleeding rate*	**EMA**	*European Medicines Agency*
AsBR	*Annualised spontaneous bleeding rate*	**EQ-5D-5L**	*Standardised measure of health-related quality of life*
ASH	*American Society of Hematology*	**F**	*Factor*
APC	*Activated protein C*	**FDA**	*Food and Drug Administration*
APTT	*Activated partial thromboplastin time*	**FVII**	*Factor VII*
AST	*Aspartate transaminase*	**FVIIa**	*Factor VII activated*
AT	*Antithrombin*	**FVIID**	*Factor VII deficiency*
ATHN	*American Thrombosis and Hemostasis Network*	**FVIII**	*Factor VIII*
AUCinf	*Area under the curve extrapolated to infinity*	**FIX**	*Factor IX*
BDD	*B-domain deleted*	**FX**	*Factor X*
BE	*Bleeding episode*	**gc/kg**	*Genome copies per kilogram*
BLA	*Biologics License Application*	**GT**	*Glanzmann Thrombasthenia*
BP	*Bodily pain / Blood pressure*	**HA**	*Haemophilia A*
BPA	*Bypassing agents*	**HB**	*Haemophilia B*
BU/ml	*Bethesda units per millilitre*	**HPPQ**	*Hemophilia Patient Preference Questionnaire*
CFB	*Change from baseline*	**INR**	*International normalised ratio*
CFC	*Clotting factor concentrates*	**IV**	*Intravenous*
CHMP	*Committee for Human Medicinal Products*	**MAD**	*Multiple-ascending dose*
CI	*Cumulative Incidence*	**nAb**	*Neutralizing antibody*
CI	*Confidence Intervals*	**OD**	*On demand*
CID	*Clinically important differences*	**OSA**	*One stage assay*
CL	*Clearance*	**PK**	*Pharmacokinetics*
Cmax	*The peak plasma concentration after drug administration*	**PwH**	*People with haemophilia*
CSA	*Chromogenic substrate assay*	**RNA**	*Ribonucleic acid*

CV	*Cardiovascular*	**SAD**	*Single ascending dose*
CVAD	*Central venous access device*	**SC**	*Subcutaneous*
CWA	*Clot waveform analysis*	**SD**	*Standard deviation*
DNA	*Deoxyribonucleic acid*	**TFPI**	*Tissue factor pathway inhibitor*
DMC	*Data Monitoring Committee*	**VWD**	*Von Willebrand disease*

Section 1 - Recent Marketing Authorisations, Indication Expansion and Early Clinical Trials

Rebalancing therapies

In May 2026, the European Commission (EC) has granted marketing authorisation for the expansion of the approved indication for Hympavzi® (marstacimab) to include patients aged 12 years and older, weighing at least 35 kg, with haemophilia A with FVIII inhibitors or haemophilia B with FIX inhibitors. In 2024, the marketing authorisation for Hympavzi® (marstacimab) had already been granted to patients aged 12 years and older, weighing at least 35 kg, with severe haemophilia A without FVIII inhibitors or severe haemophilia B without FIX inhibitors.

In June 2026, the U.S. Food and Drug Administration (FDA) has approved a label expansion for Hympavzi® (marstacimab), extending its indication to prevent or reduce bleeding episodes in patients aged 6 years and older with haemophilia A or haemophilia B, regardless of inhibitor status.

Gene therapy for haemophilia A

Following its October 2025 announcement regarding the potential divestment of Roctavian, BioMarin conducted a review to identify a qualified buyer. As no suitable buyer was identified, the company decided to voluntarily withdraw Roctavian from the market as of May 2026.

Gene therapy for haemophilia B

In June 2026, Be Biopharma discontinued an early-stage Phase 1/2 BeCoMe-9 study of its B cell therapy in haemophilia B.

Other bleeding disorders

In July 2026, the U.S. Food and Drug Administration (FDA) approved the use of Wilate® (von Willebrand Factor/Coagulation Factor VIII Complex) for routine prophylaxis to reduce the frequency of bleeding episodes in paediatric patients under six years of age with von Willebrand disease (VWD).

Section 2 - Report highlights

An Update on Novel Therapies in Haemophilia A

Factor Replacement Therapies

Efmoroctocog alfa (brand name Elocta, Eloctate®)

Interim analysis of the A-MORE real-world study: 4-year treatment outcomes with a recombinant factor VIII Fc in the overall and non-severe populations (ISTH 2026, PB3324)
In a presentation at ISTH 2026, J. Astermark et al shared the fifth interim analysis of the A-MORE real-world study (NCT04293523), reporting 4-year outcomes with efmoroctocog alfa (rFVIIIFc, Elocta/Eloctate®) prophylaxis in 423 people with hemophilia A across 14 European/Middle Eastern countries, including 38 with non-severe disease. Bleed control remained low and stable through 48 months: annualized bleed rate (ABR) held around 0.65–0.69 and annualized joint bleed rate (AJBR) around 0.41–0.42 from year 1 to year 4, with the proportion of patients experiencing zero bleeds rising from 66.9% to 74.1% and zero joint bleeds from 76.6% to 82.6%. Outcomes were slightly better in the non-severe subgroup despite similar dosing/frequency. Target joints were uncommon, largely resolved (22 of 26), and none recurred. Joint health scores (HEAD-US, HJHS) stayed essentially unchanged from baseline to 48 months. Overall, the data support sustained bleed protection and preserved joint health with long-term rFVIIIFc prophylaxis across both severe and non-severe populations.

Efanesoctocog alfa (Altuvoct, Altuviiio®)

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)
In a presentation at ISTH 2026, C. Königs et al reported results from the FREEDOM Phase 3b study, which evaluated the impact of once-weekly efanesoctocog alfa prophylaxis on joint health in patients with severe haemophilia A. In 93 participants followed for 12 months, treatment resulted in very low bleeding rates, with most patients experiencing no treated joint bleeds. Joint health assessments using the Haemophilia Joint Health Score (HJHS) and HEAD-US imaging showed modest improvements, with reductions in overall joint scores and improvements in synovial hypertrophy in a proportion of patients.

Joint Health Outcomes With Efanesoctocog Alfa Prophylaxis for Patients With Severe Hemophilia A: Third Interim Analysis of the Phase 3 XTEND-ed Study (ISTH 2026, PB3282)
In a presentation at ISTH 2026, C. Königs et al reported the third interim analysis of XTEND-ed, the long-term extension of the phase 3 XTEND-1 study, presenting 4-year joint health outcomes with once-weekly efanesoctocog alfa prophylaxis (50 IU/kg) in adults and adolescents (≥12 years) with severe hemophilia A. Among 132 participants with evaluable Hemophilia Joint Health Scores (HJHS) at XTEND-1 baseline (median total score 19), gradual improvements were seen through XTEND-ed Month 36, with the largest domain-level gains in strength and swelling; gait scores stayed essentially stable. By Month 36, 85.6% of evaluable participants (n=90) showed improved or unchanged total

HJHS scores. The authors conclude that long-term weekly efanesoctocog alfa prophylaxis continues to improve and/or maintain joint health over up to 4 years in this population.

Damoctocog Alfa Pegol (Jivi®)

Sixth Interim Analysis of the HEM-POWR Study: Real-World Effectiveness and Safety of Damoctocog Alfa Pegol in Patients With Severe and Nonsevere Hemophilia A (WFH 2026, PP-085 (291)

In a presentation at WFH 2026, M. T. Reding et al presented the sixth interim analysis of the HEM-POWR study, reporting real-world effectiveness and safety of damoctocog alfa pegol (Jivi®) in previously treated patients with severe and nonsevere hemophilia A. Among 250 patients with severe and 52 with nonsevere disease in the full analysis set, total annualized bleed rate (ABR) improved from prior FVIII treatment to damoctocog alfa pegol: from 3.0 to 2.2 in severe disease and from 1.6 to 1.0 in nonsevere disease. Safety was acceptable, with 41.1% of the 370-patient safety set experiencing any treatment-emergent adverse event and 14.1% experiencing a serious event; adverse events of special interest were rare (3 patients with severe disease: arthralgia, petit mal epilepsy, and transient resolved inhibitor development), and only 2 patients discontinued treatment (due to tendonitis and arthropathy). The authors conclude that damoctocog alfa pegol showed sustained effectiveness and an acceptable safety profile in both severe and nonsevere hemophilia A, supporting continued use.

Sixth Interim Analysis of the Real-World HEM-POWR Study: Surgical Hemostasis With Damoctocog Alfa Pegol in Patients With Hemophilia A (WFH 2026, PP-086 (297)

In a presentation at WFH 2026, M. T. Reding et al presented the sixth interim analysis of the HEM-POWR study, focusing on surgical hemostasis outcomes with damoctocog alfa pegol (Jivi®) in previously treated patients with hemophilia A. Among 370 patients in the safety analysis set (median age 36, 81.6% severe), 76 (20.5%) underwent at least one surgery during the observation period, totaling 118 surgeries (83 minor, 35 major). Damoctocog alfa pegol was used in 79.5% of minor and 80.0% of major surgeries, with mean doses per infusion of 41.8 IU/kg (minor) and 44.9 IU/kg (major). Bleeding volumes were low for minor surgeries (mean 5.7 mL) but higher for major surgeries (mean 342.8 mL), with blood transfusions required in 1.2% of minor and 14.3% of major procedures (the latter including both elective and emergency cases). The authors conclude that damoctocog alfa pegol provided effective hemostatic support for patients with hemophilia A undergoing surgery during the observation period.

Rurioctocog Alfa Pegol (Adynovi, Adynovate®)

Low Inhibitor Rate and Assessment of Binding Antibodies in Previously Untreated Patients with Severe Hemophilia A Treated with Rurioctocog Alfa Pegol: Final Results from a Prospective Phase 3 Study (ISTH 2026, PB1432)

In a presentation at ISTH 2026, S. Tangada et al presented final results from a phase 3 prospective study of rurioctocog alfa pegol (Adynovate/Adynovi®) in previously untreated patients (PUPs) with severe hemophilia A, focused on FVIII inhibitor development and binding antibodies against FVIII, PEG, and PEG-FVIII. Of 120 PUPs dosed, 11 developed FVIII inhibitors (5 low titer, 6 high titer). Among 92 inhibitor-free participants with at least 100 exposure days, 50 tested positive for IgM and/or IgG binding antibodies, with 18 positive for more than one antibody type; PEG-FVIII IgG antibodies were the most commonly detected, found in 47 inhibitor-free participants. Antibody responses varied in persistence, with some pre-existing at baseline, some persistent, and some transient. The authors conclude that despite binding antibody development in a subset of PUPs, the overall FVIII inhibitor rate with rurioctocog alfa pegol remained low.

Bispecific Monoclonal Antibodies (including FVIII Mimetics)

Emicizumab (Hemlibra®)

MRI-Based Assessment of Joint Outcomes in Children With Severe Hemophilia A on Emicizumab Prophylaxis: A Prospective Observational Study (EAHAD 2026, OR02)

In a presentation at EAHAD 2026, L.M. Sherief et al presented findings from a prospective observational study assessing MRI-based joint outcomes in children with severe hemophilia A on emicizumab prophylaxis. The study followed 39 boys (median age 8 years) across 54 index joints (knees, ankles, elbows), comparing clinical and MRI evaluations at baseline and after 12 months. After one year, mean annualized bleeding rate dropped sharply from 50 to 0.46 and mean HJHS improved from 13 to 8 (both $p<0.001$). MRI showed substantial structural gains: moderate joint effusions fell from 22.2% to 11.1%, and large effusions were eliminated entirely, synovial hypertrophy decreased from 83.3% to 61.1%, and haemosiderin deposition dropped from 66.7% to 16.7%. Osteochondral changes improved in 22.2% of joints, with progression seen in only 5.6%. Overall, 88.9% of joints showed MRI improvement and 11.1% remained stable, with none worsening. The authors conclude that emicizumab prophylaxis delivers both clinical and radiological benefits, supporting its role in limiting joint disease progression and improving long-term musculoskeletal outcomes in children with severe hemophilia A.

Pharmacokinetic and Pharmacodynamic Variability of Emicizumab in Real-World Haemophilia A Patients: Insights From a Long-Term Single-Centre Cohort Study (WFH 2026, FP-031 (482)

In a presentation at WFH 2026, A. Colombo et al presented long-term single-centre data examining pharmacokinetic and pharmacodynamic variability of emicizumab in real-world hemophilia A patients. The cohort included 40 people with hemophilia A (97.5% severe, 40% with current inhibitors, 30% under age 12) followed on emicizumab prophylaxis for a median of 5.7 years. While plasma emicizumab concentrations remained consistently in the therapeutic range (median 49 µg/mL) with corresponding FVIII-like activity well above 15 IU/dL (median 19.6 IU/dL), and the two measures correlated strongly with each other, neither correlated with time since last injection. Notably, only 30% of patients were bleed-free during follow-up, while 28 patients experienced 118 bleeding episodes (mostly joint and spontaneous bleeds); emicizumab concentration and FVIII-like activity were similar between bleeders and non-bleeders. The authors conclude that emicizumab plasma concentration and FVIII-like activity do not reliably reflect the drug's hemostatic protection and cannot be used as a proxy for bleed risk.

Inhibitor development during emicizumab prophylaxis in previously treated patients with severe hemophilia A (less than 50 exposure days) (ISTH 2026, OC 35.4)

In a presentation at ISTH 2026, V. Labarque et al reported on inhibitor development in previously treated patients with severe hemophilia A who had fewer than 50 exposure days (EDs) to FVIII when starting emicizumab prophylaxis. Using data from the international PedNet registry, the analysis identified 49 patients (median 14 EDs at emicizumab initiation) with no prior inhibitor history, followed for a median of 2.2 years. Despite reduced reliance on FVIII under emicizumab, 5 of these 49 patients (10%) developed a clinically relevant inhibitor before reaching 30 EDs (range 9–28 EDs). All five carried a high-risk genotype (four with intron 22 inversion, one with a large structural change), and none were on regular FVIII infusions while on emicizumab. The authors conclude that inhibitor development remains a relevant risk even in the emicizumab era, reinforcing the need for

continued inhibitor surveillance — though the true scale of the risk is still unclear, since most patients in the cohort had not yet accumulated enough FVIII exposure days for a full assessment.

NXT007

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)

In a presentation at ISTH 2026, M. E. Mancuso et al. reported that NXT007 prophylaxis showed favourable safety and efficacy outcomes in people with haemophilia A, with or without factor VIII inhibitors, in pooled analyses from two phase I/II multiple-ascending-dose studies. Once-monthly subcutaneous NXT007 administration resulted in very low treated annualised bleeding rates (ABR), with 85.7% of participants experiencing zero treated bleeds during the maintenance period. NXT007 demonstrated dose-dependent pharmacokinetics and increased thrombin generation, with no dose-related safety concerns, thrombotic events, or clinically relevant immunogenicity signals observed, supporting further evaluation in phase III trials.

Major Surgeries in People with Hemophilia A under NXT007 Prophylaxis: Experience from NXTAGE Phase I/II Study (ISTH 2026, OC 02.3)
In an oral presentation at ISTH 2026, K. Nogami et al. reported a case series from the phase I/II NXTAGE study describing three major surgeries performed in patients with haemophilia A on NXT007 prophylaxis. All three patients were on the 1.08 mg/kg once-every-four-weeks maintenance dose: two non-inhibitor patients (laparoscopic cholecystectomy and total elbow arthroplasty) received only a single small dose of factor VIII preoperatively, while a third inhibitor patient underwent ankle arthroscopic synovectomy using only oral tranexamic acid, without any coagulation factor products. No surgery-related bleeds or thrombotic events occurred in any case. These findings suggest NXT007 may enable major, including high-bleeding-risk orthopedic surgeries with minimal perioperative factor support, supporting its potential for hemostatic normalization, though further surgical case data are needed.

Mim8

Mim8 (denecimig) prophylaxis in adults and adolescents with haemophilia A with or without inhibitors: Interim results from the FRONTIER4 long-term safety and efficacy study (ISTH 2026, OC 02.4)

In a presentation at ISTH 2026, J. Windyga et al. reported that long-term Mim8 (denecimig) prophylaxis demonstrated sustained efficacy and a favourable safety profile in adults and adolescents with haemophilia A, with or without factor VIII inhibitors, in the phase 3/extension FRONTIER4 study. Once-weekly, once-every-two-weeks, and once-monthly subcutaneous Mim8 regimens resulted in consistently low annualised bleeding rates (ABR), with the majority of participants achieving zero treated bleeds across all dosing schedules. No thromboembolic events were reported, injection-site reactions were infrequent and mild, and no clinically relevant neutralising anti-denecimig antibody effects were observed, supporting the long-term safety and efficacy of flexible Mim8 prophylaxis regimens.

Mim8 prophylaxis in Children With Haemophilia A: 52-week Efficacy and Safety Outcomes From FRONTIER3 (EAHAD 2026, OR09)

In a presentation at EAHAD 2026, G. Kenet et al reported 52-week efficacy and safety results from FRONTIER3, a phase 3 paediatric study of Mim8 (denecimig), a next-generation activated factor VIII

mimetic bispecific antibody for subcutaneous prophylaxis in children aged 1–11 with hemophilia A. After an initial 26-week period of weekly (QW) dosing, patients could switch to monthly (QM) dosing for the second 26 weeks; of 70 completers, 32 (45.7%) chose QM while 38 remained on QW. Mim8 was well tolerated across both regimens: no severe adverse events, thromboembolic events, or hypersensitivity reactions occurred, injection site reactions were infrequent (0.9% of QW injections, 2.6% of QM injections), and none of the 5 patients with anti-Mim8 antibodies showed neutralizing activity. Bleed protection was robust, with estimated mean annualized bleed rates in Part 2 of 0.42 for QW and 0.25 for QM, and zero treated bleeds in 81.6% of QW and 87.5% of QM patients; no patients with inhibitors reported treated bleeds, and all 10 baseline target joints resolved by week 52. The authors conclude that both weekly and monthly Mim8 dosing provided strong, well-tolerated bleed protection in children with hemophilia A, and all study completers opted to continue into the FRONTIER4 open-label extension.

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)

In a presentation at ISTH 2026, M. Carcao et al reported interim safety and efficacy results from FRONTIER4, the long-term extension study following children with hemophilia A (with or without inhibitors) who continued denecimig (Mim8) prophylaxis after completing FRONTIER3, either maintaining weekly (QW) or monthly (QM) dosing or newly starting once-every-two-weeks (Q2W) dosing. Among 61 boys (mean age 6 years, 90.2% severe, 23.0% with inhibitors), safety remained favorable over 839 injections: no thromboembolic events or hypersensitivity reactions occurred, injection site reactions were rare (2.0%) and mild, and there was no clinical evidence of neutralizing anti-denecimig antibodies. Bleed protection was strong across all regimens, with estimated mean annualized bleed rates of 0.50 (QW), 0.37 (QM), and zero treated bleeds observed with Q2W; 85.2%, 88.5%, and 100.0% of children on QW, QM, and Q2W respectively had zero treated bleeds. Outcomes were similarly low regardless of inhibitor status. The authors conclude these interim findings reinforce FRONTIER3 results, supporting denecimig's safety and efficacy in children across dosing frequencies and inhibitor status.

INNO8

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

In a presentation at ISTH 2026, L. Ingemann et al. presented the first data on Inno8, the first orally administered factor VIII mimetic, in healthy male participants. Inno8 is a bispecific nanobody fragment formulated with an absorption enhancer (SNAC) to enable oral bioavailability for hemophilia A prophylaxis. The trial included both single ascending intravenous doses and multiple ascending oral doses over 10 days, compared against placebo. No serious or severe adverse events occurred, and no anti-drug antibodies were detected. Pharmacokinetics were dose-proportional across both routes of administration, and dose-dependent effects were seen on clotting markers such as aPTT and thrombin generation. Overall, Inno8 was safe and well tolerated at all tested doses, and these results support continued clinical development of an oral prophylactic option for hemophilia A which would be a potential alternative to current injectable treatments.

Gene Therapy

Valoctocogene Roxaparvovec (Roctavian®)

Characterization of ALT Elevations During the 5-Year GENEr8-1 Trial of Valoctocogene Roxaparvovec Gene Transfer for Severe Hemophilia A (EAHAD 2026, OR16)

In a presentation at EAHAD 2026, R. Klamroth et al presented 5-year data from the GENEr8-1 trial characterizing alanine aminotransferase (ALT) elevations following valoctocogene roxaparvovec (Roctavian®) gene therapy in 134 participants with severe hemophilia A. ALT elevations were most frequent and pronounced in Year 1 post-infusion, with 297 events in 78.4% of participants, all of whom received glucocorticoids; rates then declined and stabilized in subsequent years (Year 2: 29.1% of participants; Years 3–5: 15.4–17.8%), with glucocorticoid initiation limited to Year 2 (33.6%) and none thereafter. Across the 5 years, most elevations were mild (65.0% were 1–1.5x the upper limit of normal), with severe elevations (>5x ULN) confined to the first two years and none occurring afterward. The authors conclude that ALT elevations following valoctocogene roxaparvovec gene transfer were generally transient and mild, peaking in Year 1 before decreasing and stabilizing, contributing to the therapy's overall safety profile characterization.

ΔSQ-F309S-X5

Vastly Improved Hepatic AAV Gene Therapy for Hemophilia A Using Engineered Factor VIII Combination Variants with Minor Amino Acid Changes (ISTH 2026, OC 18.4)

In a presentation at ISTH 2026, R. Herzog et al presented preclinical data on engineered factor VIII (FVIII) variants designed to improve hepatic AAV gene therapy for hemophilia A. Building on prior variants addressing ER stress, secretion efficiency, and proteolytic stability, the team tested 10 combination variants in hemophilia A mouse models. The ΔSQ-F309S-X5 variant emerged as the strongest candidate, achieving 6–9 fold higher expression than standard B-domain-deleted FVIII (BDD-WT), with stable expression in the normal physiological range sustained over 4–6 months at reduced vector doses and without inducing inhibitors, even in inhibitor-prone and BDD-tolerant mouse strains. In primary human hepatocytes, this variant was synthesized and secreted more efficiently, aggregated less, and triggered lower cellular stress responses than BDD-WT. Separately, X5-QQ combination variants achieved superphysiological expression levels, though the authors note these may carry greater interpatient variability and thrombotic risk. The authors conclude that ΔSQ-F309S-X5 represents a strong translational candidate for substantially improved hemophilia A gene therapy.

BS7189-HSA

A Novel AAV-Mediated Gene Therapy for Hemophilia A Using a FVIII-Mimetic Trispecific VHH antibody (ISTH 2026, OC 18.1)

In a presentation at ISTH 2026, R. Liu et al presented a novel AAV-mediated gene therapy approach for hemophilia A using a compact FVIII-mimetic trispecific VHH antibody, designed to overcome the packaging, dosing, durability, and inhibitor-related limitations of conventional FVIII gene transfer. The engineered antibody, BS7189-HSA (38 kDa, targeting activated factor IX, factor X, and human serum albumin for half-life extension), restored thrombin generation in FVIII-deficient plasma roughly 10-fold more potently than emicizumab-SIA. Repeated dosing in non-human primates showed no anti-drug antibodies or adverse effects. When delivered via a liver-targeted AAV8 vector, a single

dose produced sustained therapeutic serum levels for at least 24 weeks in mice, and robust, persistent expression in non-human primates without hepatotoxicity, cytokine elevation, or other treatment-related pathology. The authors conclude that this liver-directed AAV-delivered FVIII-mimetic antibody offers a promising next-generation approach to durable hemostatic correction in hemophilia A, effective regardless of FVIII inhibitor status.

An Update on Novel Therapies in Haemophilia B

Factor Replacement Therapies

Eftrenonacog alfa (Alprolix®)

Final Surgery Data from B-MORE: A 24-Month, Prospective, Non-Interventional Study of the Real-World Effectiveness and Usage of rFIXFc in Haemophilia B (ISTH 2026, PB2117)

In a presentation at ISTH 2026, H. Glosli et al presented final surgical data from the B-MORE study, a 24-month prospective, non-interventional evaluation of eftrenonacog alfa (rFIXFc, Alprolix) in people with hemophilia B (PwHB) across Europe and the Middle East. Among 151 PwHB enrolled, 32 underwent a total of 52 surgeries (10 major, 42 minor). For major surgeries, median rFIXFc consumption was 134.2 IU/kg to 24 hours post-surgery and 227.1 IU/kg to 72 hours, with hemostatic efficacy rated excellent/good in all evaluable cases and median hospitalization of 6 days. For minor surgeries, median consumption was lower (66.7 IU/kg to 24 hours, 81.7 IU/kg to 72 hours), with excellent/good efficacy in the large majority of evaluable cases, no reported blood loss, and median hospitalization of 2 days. No inhibitor development or surgery-related serious adverse events were reported. The authors conclude that real-world B-MORE data confirm rFIXFc is highly effective and well tolerated for perioperative management in people with hemophilia B.

Gene Therapy

Dalnacogene Ponparvovec (BBM-H901)

Safety and Efficacy of Dalnacogene Ponparvovec (BBM-H901) in Moderate to Severe Adult Hemophilia B Participants: Long Term Follow-Up Data in an Early Phase Pilot Study (WFH 2026, FP-014 (77)

In a presentation at WFH 2026, F. Xue et al presented long-term follow-up data from an early-phase pilot study of dalnacogene ponparvovec (BBM-H901), an AAV-based gene therapy using a liver-tropic AAV843 capsid and a hyperactive Padua FIX variant, in adults with moderate to severe hemophilia B. Among 10 participants dosed between 2019 and 2021 (median follow-up 235.5 weeks, three reaching 5 years), FIX activity remained stable and durable, with a mean level of 40.95% at each patient's latest follow-up; 9 of 10 participants discontinued FIX replacement entirely, and one resumed exogenous FIX after a decline below 5% at week 130. Median target joint count fell from 1.5 to 0, and no liver toxicity, drug-related adverse events, FIX inhibitors, thrombosis, or malignancies were reported over the long-term follow-up (He reported 76% having a FIX expression >40%,/ 20% <40%,/ 10% <20%/ 5% <10% / 2% <5%, 84% had ABR of 0). The authors conclude that dalnacogene ponparvovec provided durable bleeding protection for up to 5 years post-treatment and was generally well tolerated.

Etranacogene dezaparvovec (Hemgenix®)

Durable Bleed Protection for all Bleeding Subtypes and Favorable Safety Over 5 Years (end-of-study) in the Phase 3 HOPE-B Trial for Persons With Severe or Moderately Severe Haemophilia B (EAHAD 2026, OR11)

In the oral presentation at EAHAD 2026, F. W. G. Leebeek et al reported the results from the the Phase 3 HOPE-B Trial for Persons With Severe or Moderately Severe Haemophilia B. Five-year HOPE-B trial follow-up demonstrated lasting efficacy, including a sustained reduction in FIX-treated bleeds, and a favorable safety profile.

Durable efficacy and safety in responders: 5-Year post hoc end-of-study analysis of etranacogene dezaparvovec in the phase 3 HOPE-B trial in patients with severe/moderately severe haemophilia B (ISTH 2026, OC 21.4)

In a presentation at ISTH 2026, C. Hermans et al reported a 5-year post hoc analysis of the HOPE-B trial in adults with severe/moderately severe haemophilia B. Among the 52 responders (96% of enrollees), endogenous factor IX activity remained stable from month 6 through year 5 (39.0 to 36.1 IU/dL), while annualised bleeding rates dropped significantly across all bleed subtypes (82–90% reductions versus lead-in) and exogenous FIX use fell by 98%. Only one participant (2%) returned to continuous prophylaxis, and the therapy maintained a favourable long-term safety profile with no serious treatment-related adverse events, oncogenicity, or late hepatotoxicity.

CSL220

Stable Factor IX Expression and Sustained Reductions in Factor IX Use 9 Years After Gene Therapy With CSL220 in Adults With Haemophilia B (EAHAD 2026, OR12)

In a presentation at EAHAD 2026, W. Miesbach et al presented 9-year follow-up data from the Phase I/II(b) study of CSL220 (formerly AMT-060), an AAV5 vector encoding codon-optimized wild-type FIX, in adults with hemophilia B. Among patients continuing in the extension study without returning to prophylaxis (Cohort 1, lower dose, n=3; Cohort 2, higher dose, n=5), endogenous FIX activity remained stable at Year 9 (median 5.0 IU/dL in Cohort 1, 5.7 IU/dL in Cohort 2). Bleeding control was better maintained in the higher-dose Cohort 2, with mean annualized bleeding rate of 1.1 versus 3.6 in Cohort 1, and annualized spontaneous bleeding rate of 0.3 versus 2.3. FIX consumption remained low in both cohorts (3,644 IU/year in Cohort 2 versus 13,067 IU/year in Cohort 1). No new safety events emerged during Year 9, and no patient resumed continuous FIX prophylaxis. The authors conclude that this 9-year follow-up supports the durability, stability, and safety of FIX expression after CSL220 gene therapy, particularly at the higher dose selected for Phase 3 development, with findings considered potentially indicative of the closely related successor product, etranacogene dezaparvovec (CSL222).

An Update on Rebalancing Therapies

Concizumab (Alhemo®)

Concizumab prophylaxis in paediatric participants with haemophilia A/B with inhibitors in the phase 3 explorer10 study: Efficacy, safety and PK/PD results from the 32-week cut-off (ISTH 2026, OC 02.1)

In a presentation at ISTH 2026, S. Šaulytė Trakymienė et al. reported 32-week results from the phase 3 explorer10 study evaluating prophylaxis in 24 paediatric participants (under 12 years) with haemophilia A or B with inhibitors. Daily subcutaneous concizumab reduced the annualised bleeding rate by 82% compared to previous on-demand treatment (2.08 vs 11.51), with over half the participants experiencing zero treated bleeds during the study period. Concizumab plasma concentrations and pharmacodynamic markers remained stable, and the therapy was well tolerated, with a safety profile consistent with previous observations in older patients and no thromboembolic events. 29% had anti-drug antibodies which had no clinical impact. There were no cases of thrombosis seen. The findings support concizumab prophylaxis as an effective bleed-prevention option in this younger inhibitor population.

Marstacimab (Hympavzi®)

Health-Related Quality of Life Outcomes for Marstacimab in Participants With Severe Hemophilia A or Moderately Severe to Severe Hemophilia B With Inhibitors: Results From the Phase 3 BASIS Trial (WFH 2026, FP-010 (214)

In a presentation at WFH 2026, J. Mahlangu et al reported the results from the Phase 3 BASIS Trial. The study shows that marstacimab produced clinically relevant and statistically significant improvements in HRQoL, functional status, and patient-perceived benefit in HA/HB participants with inhibitors.

Joint Health in Participants With Hemophilia A or B With Inhibitors Treated With marstacimab in the Phase 3 BASIS Trial (EAHAD 2026, OR08)

In a presentation at EAHAD 2026, J. Mahlangu et al reported joint health outcomes from the phase 3 BASIS trial evaluating marstacimab, a tissue factor pathway inhibitor-targeting monoclonal antibody, in participants with hemophilia A or B and inhibitors. Among 60 participants with inhibitors (47 with hemophilia A, 13 with hemophilia B; median age 23), 71.7% had at least one target joint at study entry. In the on-demand subgroup (n=48), switching from bypassing agents to once-weekly subcutaneous marstacimab reduced annualized bleeding rate for treated joint bleeds by 93% (from a model-based mean of 15.15 to 1.10) and for treated target joint bleeds by 88% (from 6.42 to 0.79). Mean target joint count fell from 0.6 to effectively zero over 12 months, and Hemophilia Joint Health Score showed an early, modest improvement trend that did not reach statistical significance. The authors conclude that marstacimab markedly reduced joint and target joint bleeding and eliminated most target joints over 12 months, supporting it as a promising prophylactic option for patients with inhibitors at risk of progressive joint damage, with longer-term joint health effects to be assessed in the open-label extension study.

Marstacimab prophylaxis in pediatric participants with hemophilia A or B with or without inhibitors: interim results from the phase 3 BASIS KIDS trial (ISTH 2026, LB 02.1)

In a presentation at ISTH 2026, G. Kenet et al reported interim results from the phase 3 BASIS KIDS trial evaluating prophylaxis in 92 pediatric participants (median age 10) with hemophilia A or B, with or without inhibitors. Weekly subcutaneous marstacimab substantially reduced annualized treated bleeding rates compared to historical treatment: a 92.4% reduction versus on-demand therapy in the inhibitor cohort, and a 48.1% reduction versus routine prophylaxis in the non-inhibitor cohort. The safety profile was favourable, with adverse events mostly mild-to-moderate, only 2 serious AEs, and no deaths, thrombotic events, or treatment discontinuations due to adverse events. These findings support marstacimab's efficacy and safety in children, consistent with prior results in adolescents and adults.

An Update on Novel Therapies in VWD and Other Bleeding Disorders

Vonicog alfa (Veyvondi, Vonvendi®)

Recombinant von Willebrand Factor Prophylaxis for Severe von Willebrand Disease: Final Results Focusing on Adults Receiving Once Weekly Prophylaxis in a Phase 3b Continuation Study (EAHAD 2026, OR14)

In a presentation at EAHAD 2026, S. Susen et al presented final results from a Phase 3b continuation study of recombinant von Willebrand factor (rVWF) prophylaxis in adults with severe VWD, focusing on a post hoc analysis of once-weekly (QW) dosing. Among 14 adult participants overall, 5 received QW rVWF prophylaxis (2 rollover from a prior Phase 3 study, 3 non-rollover; median age 35, mostly Type 2A VWD), all completing 35–36 months of treatment. Median 12-month annualized spontaneous bleeding rate on QW dosing was 1.0, similar to the full prophylaxis cohort; non-rollover patients saw reduced bleeding compared with their prior on-demand treatment, while rollover patients maintained the same low bleeding rate seen in the parent study. Mean weekly dose was 63.8 IU/kg over roughly 1.1 infusions, and only 2 of 5 patients required escalation to twice-weekly dosing for breakthrough bleeds after about 2 years. No rVWF-related adverse events, hypersensitivity reactions, thromboembolic events, or inhibitor development occurred. The authors conclude that once-weekly rVWF prophylaxis can be an effective treatment option with a favorable safety profile for adults with severe VWD.

HMB-002

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

In a presentation at ISTH 2026, P. Raheja et al reported the results from the first-in-human investigation of HMB-002. The study shows that HMB-002 was well-tolerated and produced sustained dose-dependent increases in pharmacokinetics and pharmacodynamics (VWF and FVIII), supporting proof of mechanism and the potential for infrequent subcutaneous dosing. Her presentation included data on VWD type 1, 2A and 3. Both males and females aged 18-65 wit a prior ABR of at least 3 were included. No thrombosis seen. ATBR decreased from 20.1-1.6

HMB-003

A long-acting peptide plasmin inhibitor with extended antifibrinolytic activity enabling once-per-cycle subcutaneous treatment for heavy menstrual bleeding: Preclinical development of HMB-003 (ISTH 2026, OC 05.1)

In a presentation at ISTH 2026, H. Østergaard et al presented preclinical development data for HMB-003, a long-acting peptide plasmin inhibitor designed for once-per-cycle subcutaneous treatment of heavy menstrual bleeding. Unlike tranexamic acid, which inhibits plasminogen activation and requires thrice-daily dosing, HMB-003 directly inhibits plasmin at its active site and achieves half-life extension via fatty diacid conjugation and reversible albumin binding. In vitro studies showed sub-nanomolar plasmin affinity and concentration-dependent, selective inhibition of fibrinolysis (IC_{50} 1–5 µM) without affecting thrombin generation or platelet aggregation. In minipigs, subcutaneous dosing produced peak levels within a day and a terminal half-life of 153 hours, with intravenous dosing achieving complete fibrinolysis inhibition for 7 days before gradually returning to baseline. In a mouse injury model, HMB-003 dose-dependently restored fibrin accumulation at injury sites. The authors conclude that HMB-003's potent, selective antifibrinolytic activity and pharmacokinetic profile support sustained hemostatic coverage from a single subcutaneous dose across a menstrual cycle, warranting further development as a non-hormonal antifibrinolytic therapy.

HMB-003, a long-acting peptide plasmin inhibitor, potently inhibits fibrinolysis and localizes with fibrin in a human whole blood microfluidic flow model (ISTH 2026, OC 09.5)

In a presentation at ISTH 2026, M. Zivkovic et al presented data characterizing HMB-003, a long-acting peptide plasmin inhibitor in development for heavy menstrual bleeding, in a human whole blood microfluidic flow model designed to mimic physiological hemostasis. Using fluorescently labeled platelets and fibrin under flow conditions with tissue plasminogen activator-induced fibrinolysis, HMB-003 inhibited fibrinolysis in a concentration-dependent manner with a mean IC50 of 2 µM, roughly 30-fold more potent than tranexamic acid (IC50 67 µM). A plasmin-binding-deficient analog of HMB-003 showed no antifibrinolytic effect, confirming that activity depends on direct plasmin engagement, and fluorescently labeled HMB-003 was shown to colocalize with fibrin within the formed clot. The authors conclude that HMB-003 potently inhibits fibrinolysis under flow conditions relevant to human hemostasis, with fibrin colocalization consistent with its ability to inhibit both free and fibrin-bound plasmin, supporting continued development as a novel antifibrinolytic agent for heavy menstrual bleeding.

SR604

Clinical evaluation of SR604, a novel anti–activated protein C antibody, for prophylactic treatment of hemophilia and factor VII deficiency (ISTH 2026, OC 32.4)

In a presentation at ISTH 2026, R. Yang et al presented Phase I/IIa results for SR604, a monoclonal antibody that selectively blocks activated protein C, evaluated as a broad-spectrum prophylactic therapy for hemophilia A/B and congenital factor VII deficiency. Across both phases, SR604 was well tolerated with no serious or thrombotic events and linear pharmacokinetics; low-titer anti-drug antibodies appeared in a small number of patients without safety impact. Phase IIa prophylaxis (24 patients, biweekly dosing) produced substantial reductions in total, spontaneous, and joint annualized bleeding rates, with one FVII-deficient patient bleed-free over 24 weeks. The authors conclude SR604 shows excellent safety and meaningful prophylactic efficacy, supporting it as a long-acting, broad-spectrum option for congenital bleeding disorders, with a Phase IIb trial now testing extended dosing intervals.

Sutacimig

Sutacimig Prophylaxis in Glanzmann Thrombasthenia: Results from a Phase 2 Long-Term Extension (ISTH 2026, OC 57.3)

In a presentation at ISTH 2026, Q. Van Thillo et al reported results from a Phase 2 long-term extension study of sutacimig, a novel bispecific antibody that binds endogenous factor VIIa and localizes it to activated platelets via TLT-1, being developed as prophylactic therapy for Glanzmann thrombasthenia (GT) — a condition with no currently approved prophylactic option. Among 34 adults enrolled across four dosing cohorts (median age 40.5, median exposure 6.9 months), the treatment period showed a 47% reduction in annualized treated bleeding rate (ATBR) from a baseline of 42.0, with the weekly dosing cohort achieving an 87% reduction and seven participants reaching 100% ATBR reduction; benefit was seen across dose levels, bleed types, and with extended treatment. Three participants underwent surgical or dental procedures with successful hemostatic outcomes. Safety was generally favorable, with predominantly mild-to-moderate adverse events, though three treatment-related grade 2 thromboembolic events occurred (a proximal DVT at the highest dose, an isolated distal DVT, and a subsegmental PE), each in the presence of other concurrent risk factors and managed with anticoagulation. The authors conclude that these safety and efficacy findings continue to support sutacimig's potential as the first prophylactic option for GT, informing dose selection and design for planned Phase 3 development.

VGA039

Subcutaneous Four-Week Dosing of the Novel Protein S Antibody VGA039 Demonstrates Safety and Clinically Meaningful Bleed Reduction in Patients With Von Willebrand Disease: Phase 1/2 Multi-Dose Study Results (WFH 2026, FP-006 (389)

In a presentation at WFH 2026, J. Mason et al reported results from a phase 1/2 multi-dose study of VGA039, a fully human IgG4 monoclonal antibody that inhibits Protein S cofactor activity to enhance thrombin generation, administered subcutaneously every four weeks in patients with von Willebrand disease (VWD). Among 16 participants across all VWD types, receiving a loading dose followed by up to 5 maintenance doses (either a flat 225 mg dose or weight-banded doses of 262.5 mg or 450 mg), VGA039 achieved plasma concentrations within the anticipated therapeutic range, with no serious drug-related adverse events or clinically significant D-dimer elevations. Among the 8 participants who completed the treatment period, bleeding reductions of 41%–100% were observed, and all completers elected to continue into the open-label extension. The authors conclude that four-weekly subcutaneous VGA039 was safe, well tolerated, and associated with clinically meaningful bleed reduction across VWD subtypes, supporting the ongoing Phase 3 trial.

Pilot Study Exploring the Lived Experiences of Adolescents and Adults With von Willebrand Disease Treated With VGA039 and Their Families in the VIVID-3 Phase 1/2 Clinical Study (WFH 2026, PP-370 (404)

In a presentation at WFH 2026, S. Nataraj et al described a qualitative pilot study exploring the lived experiences of adolescents and adults with von Willebrand disease (VWD) and their families participating in the VIVID-3 phase 1/2 trial of VGA039, an investigational once-monthly subcutaneous monoclonal antibody targeting Protein S. The non-interventional study involves semi-structured interviews with up to three VIVID-3 participants and one caregiver, analyzed thematically to capture domains such as bleeding burden, emotional and physical wellbeing, social and work/school functioning, daily activities, quality of life, family impact, and treatment perceptions. As this is a study protocol/early-stage report, specific thematic findings are not yet available and will be presented at the congress. The authors conclude that this qualitative approach will provide patient-centered context around VGA039 as a novel once-monthly subcutaneous therapy, helping

capture impact domains not fully addressed by standard clinical trial outcome measures and informing future patient-centered research in VWD.

Section 3 - Research Abstracts and Articles

Haemophilia A

Factor Replacement Therapies

Efmoroctocog alfa (brand name Elocta, Eloctate®)

Interim analysis of the A-MORE real-world study: 4-year treatment outcomes with a recombinant factor VIII Fc in the overall and non-severe populations (ISTH 2026, PB3324)

J. Astermark et al

Background: The A-MORE study evaluates the long-term effectiveness of extended half-life efmoroctocog alfa (rFVIIIFc) prophylaxis on joint health in people with hemophilia A (PwHA).

Aims: To report treatment outcomes across 4 years in the overall and non-severe populations.

Methods: A-MORE (NCT04293523) is an ongoing, prospective, non-interventional study of rFVIIIFc prophylaxis in 14 European/Middle Eastern countries. Informed consent and ethical approval were obtained. In the fifth interim analysis (cutoff: August 29, 2025), bleed rates were investigated with Negative Binomial Regression. Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and Hemophilia Joint Health Score (HJHS) were estimated via Mixed Model Repeated Measures.

Methods: Of 423 PwHA, 38 had non-severe hemophilia (Table 1). Median (interquartile range) observation time was 38.4 (30.0–44.1) months in the overall population and 39.2 (31.2–46.6) months in the non-severe subgroup. Annualized bleed rate (ABR) and annualized joint bleed rate (AJBR) remained low through 48 months, and were slightly lower in the non-severe versus overall populations despite comparable doses and injection frequencies (Table 2). In the overall population during year 1 (n=414) and year 4 (n=201), model-based mean (95% confidence interval) ABR was 0.69 (0.56–0.85) and 0.65 (0.46–0.91), and AJBR was 0.42 (0.33–0.54) and 0.41 (0.27–0.63), respectively. During the same periods, 66.9% and 74.1% of PwHA experienced zero bleeds, and 76.6% and 82.6% experienced zero joint bleeds. Of 21 target joints (n=14 PwHA) at enrollment, four were in non-severe PwHA (n=3). Another five target joints (n=4) developed during the study (none in non-severe PwHA). Of the 26 target joints (n=17), 22 (n=13) resolved. There were no recurring target joints. Joint health assessments remained stable throughout the observation period. In the overall population, at baseline and at 48 months, least-squares mean (standard error) HEAD-US (n=162) was 8.5 (0.9) and 8.5 (1.0), and HJHS (n=191) was 10.2 (1.3) and 10.3 (1.3), respectively.

Conclusions: The fifth interim analysis demonstrates that rFVIIIFc prophylaxis provides sustained protection against bleeding and supports maintenance of joint status for PwHA in the overall and non-severe populations of A-MORE.

Efanesoctocog alfa (Altuvoct, Altuviiio®)

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)

C. Königs et al

Background: Efanesoctocog alfa is a first-in-class, high-sustained factor VIII replacement therapy (ultra-long half-life FVIII).

Aims: To report 12-month interim joint health and efficacy data from FREEDOM (NCT05817812), a prospective, 24-month, Phase 3b study in patients with severe haemophilia A receiving efanesoctocog alfa prophylaxis.

Methods: Previously treated patients (≥12 years) with severe haemophilia A received once-weekly 50 IU/kg efanesoctocog alfa. Joint health was assessed using the Haemophilia Joint Health Score (HJHS) and Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). Synovial hypertrophy (SH) was defined at the patient level (≥1 joint with HEAD-US SH score of 1–2) and joint level (SH scores of 1–2). SH changes are reported as reduction (≥1 joint with ≥1-point HEAD-US SH score reduction at Month 12) or resolution (all SH-affected joints at baseline reaching scores of 0 at Month 12). Data cut: 21/07/2025. Patients provided informed consent; FREEDOM was approved by an independent ethics committee.

Results: FREEDOM enrolled 93 patients; 91 remained at Month 12. Table 1 presents total/joint annualised bleeding rates and patients with zero bleeds. Mean (SD) HJHS total scores were 13.0 (17.6) at baseline (n=83) and 11.5 (16.7) at Month 12 (N=85); mean change (SD) from baseline among patients with both assessments (N=78) was −1.1 (4.4). Mean (SD) HEAD-US total scores were 9.8 (11.4) at baseline (N=88) and 8.6 (10.5) at Month 12 (N=85); mean change (SD) among patients with both assessments (N=82) was 0.0 (2.8). At baseline, 53.8% (n=50/93) patients had HEAD-US SH in ≥1 joint, versus 45.1% (n=41/91) at Month 12. Among 47 patients with ≥1 SH-affected joint at baseline and assessment at Month 12, 25 (53.2%) had score reduction or resolution; 19.1% (n=9/47) achieved full resolution. Of joints with SH at baseline, 44.4% (n=48/108) had reduction or resolution of scores at Month 12.

Conclusions: Efanesoctocog alfa prophylaxis was highly effective in preventing joint bleeds; most patients had no treated joint bleeds over 12 months. Despite previous FVIII prophylaxis, ~half of patients entered FREEDOM with SH in ≥1 joint; of these, ~half had SH reduction or resolution after 12 months of efanesoctocog alfa.

Joint Health Outcomes With Efanesoctocog Alfa Prophylaxis for Patients With Severe Hemophilia A: Third Interim Analysis of the Phase 3 XTEND-ed Study (ISTH 2026, PB3282)

C. Königs et al

Background: Efanesoctocog alfa is a first-in-class, high-sustained factor VIII replacement therapy that overcomes the von Willebrand factor–imposed half-life ceiling. XTEND-1 (NCT04161495) showed once-weekly efanesoctocog alfa was well tolerated in adults/adolescents with severe hemophilia A, providing superior bleed prevention over prior factor VIII prophylaxis. Participants completing the XTEND-1 trial could continue weekly efanesoctocog alfa (50 IU/kg) in XTEND-ed (NCT04644575) arm A.

Aims: To report long-term joint health with efanesoctocog alfa in adults/adolescents aged ≥12 years from XTEND-1 baseline through XTEND-ed third-interim analysis (data cut: 21 February 2025).

Methods: Participants provided informed consent; the study was approved by applicable review boards. Change in Hemophilia Joint Health Score (HJHS; range 0–124) from parent study (XTEND-1) baseline up to XTEND-ed Month 36 are presented descriptively. Higher HJHS scores denote worse joint health. Individual joints (left/right elbows, knees, ankles) were scored according to 8 HJHS domains to obtain total joint score; gait score ranged from 0 to 4. Improved/worsened HJHS scores were defined by decreases/increases of ≥4 points, and unchanged (or constant) scores between -3 and +3 points.

Results: In total, 132/146 participants had evaluable HJHS scores at XTEND-1 baseline; median (range) total HJHS score was 19 (0–98) (mean [SD]: 20.5 [18.4]). For participants with an evaluable change in HJHS total score at 12-monthly intervals (Figure), gradual improvements were observed over 4 years of efanesoctocog alfa prophylaxis, from XTEND-1 baseline to XTEND-ed Month 36. At Month 36, the greatest changes in domain scores from XTEND-1 baseline were observed for strength -0.6 (2.6) and swelling -0.5 (1.7) (Table). Mean (SD) HJHS gait scores remained constant: XTEND-1 baseline, 1.7 (1.6); Month 36, 1.5 (1.6). By XTEND-ed Month 36, HJHS total score improved or remained constant in 85.6% of evaluable participants (n=90).

Conclusions: Long-term once-weekly prophylaxis with efanesoctocog alfa for up to 4 years continues to improve and/or maintain joint health in adults and adolescents with severe hemophilia A.

Damoctocog Alfa Pegol (Jivi®)

Sixth Interim Analysis of the HEM-POWR Study: Real-World Effectiveness and Safety of Damoctocog Alfa Pegol in Patients With Severe and Nonsevere Hemophilia A (WFH 2026, PP-085 (291)

M. T Reding et al

Introduction and Objective: Damoctocog alfa pegol is an extended half-life factor VIII (FVIII) product used to manage hemophilia A in previously treated patients (PTPs) aged ≥ 12 years; recent approval was received for children aged ≥ 7 years. This updated subgroup analysis of the HEM-POWR study presents effectiveness and safety data for PTPs with severe and nonsevere (mild/moderate) hemophilia A.

Materials and Methods: HEM-POWR (NCT03932201) is Phase 4, ongoing study of PTPs aged ≥ 12 years receiving prophylactic/on-demand damoctocog alfa pegol. Primary endpoint was annualized bleeding rate (ABR). PTPs with a first-documented dose of damoctocog alfa pegol, bleeding data, and ≥ 1 documented infusion in the patient diary were included in the full analysis set (FAS); modified FAS (mFAS) included those with ≥ 90 days of observation data in the patient diary. Safety, a secondary endpoint, was evaluated in the safety analysis set (SAF) which included PTPs with signed consent and ≥ 1 study dose during the observation period.

Results: At data cutoff (June 5, 2025), 250 patients with severe and 52 with nonsevere disease were included in the FAS. Median observation period for patients with severe disease was 957.5 and nonsevere was 1072.5 days. Median age (quartile 1, quartile 3) for patients with severe disease was 35.0 (22.0, 47.0) and nonsevere was 42.0 (27.0, 59.0) years. In the mFAS (N = 279), mean (standard deviation) ABR for total bleeds with previous FVIII product within 12 months prior to damoctocog

alfa pegol initiation was 3.0 (6.1) for severe disease (n = 226; missing n = 4) and 1.6 (2.5) for nonsevere (n = 49) (Figure 1). During the observation period, total ABR with damoctocog alfa pegol was 2.2 (4.9) for severe disease and 1.0 (1.3) for nonsevere. In the SAF (N = 370), there were 152 (41.1%) patients with any treatment-emergent adverse event (TEAE); 52 (14.1%) had serious TEAs. Three patients (0.8%) with severe disease had adverse events of special interest including arthralgia, petit mal epilepsy, and inhibitor development (transient and resolved). Two patients (0.5%) who had severe disease discontinued treatment due to tendonitis and arthropathy.

Conclusions: Damoctocog alfa pegol demonstrated sustained effectiveness and acceptable safety profile in PTPs with severe and nonsevere hemophilia A, supporting continued use for re treatment.

Sixth Interim Analysis of the Real-World HEM-POWR Study: Surgical Hemostasis With Damoctocog Alfa Pegol in Patients With Hemophilia A (WFH 2026, PP-086 (297)

M. T Reding et al

Introduction and Objective: Damoctocog alfa pegol, an extended half-life factor VIII (FVIII) product, is approved for management of hemophilia A in previously treated patients (PTPs) aged ≥ 7 years. The HEM-POWR study evaluates real-world effectiveness and safety in PTPs aged ≥ 12 years. Here we present data from the sixth interim analysis of HEM-POWR for surgical hemostasis during the observation period.

Materials and Methods: HEM-POWR (NCT03932201) is a Phase 4 study of prophylactic/on-demand damoctocog alfa pegol in PTPs. Secondary endpoints included assessment of surgical hemostasis measured by number of infusions and consumption of FVIII product. Safety analysis set (SAF) included patients who provided informed consent and received ≥ 1 dose of damoctocog alfa pegol in the observation period. Physicians recorded surgery data; statistics were descriptive.

Results: At data cutoff (June 5, 2025), there were 370 PTPs in the SAF. Median observation period was 909.5 days. The median age was 36 years and 81.6% of PTPs had severe hemophilia A (missing n = 4) at initial diagnosis. Most PTPs (> 90%) received prophylaxis before and during the study. In the SAF, 76 (20.5%) PTPs had ≥ 1 surgery during the observation period (Figure 1). Of 118 surgeries, 83 (70.3%) were minor and 35 (29.7%) were major surgeries (Table 1). Mean (standard deviation [SD]) total bleeding volume for minor surgeries was 5.7 (11.3; missing n = 76) mL; 1 (1.2%) elective and minor surgery (tooth extraction) required a blood transfusion. Total bleeding volume for major surgeries was 342.8 (401.7; missing n = 27) mL. Five (14.3%) major surgeries required blood transfusions; 3 were elective (hip arthroplasty, laparoscopic sleeve gastrectomy) and 2 were emergency surgeries (renal embolization, spontaneous abdominal bleeding). FVIII products were used for 69/83 (83.1%; missing n = 1) minor and 32/35 (91.4%) major surgeries; damoctocog alfa pegol was used for 66/83 (79.5%; missing n = 1) minor and 28/35 (80.0%) major surgeries. Mean (SD) number of infusions was 3.8 (4.6) for minor surgeries and 2.5 (4.1) for major. Mean (SD) dose per infusion per kg for damoctocog alfa pegol was 41.8 (14.0) international units (IU)/kg for minor and 44.9 (16.8) IU/kg for major surgeries.

Conclusions: Damoctocog alfa pegol demonstrated hemostasis in PTPs with hemophilia A who had surgeries during the observation period.

Rurioctocog Alfa Pegol (Adynovi, Adynovate®)

Low Inhibitor Rate and Assessment of Binding Antibodies in Previously Untreated Patients with Severe Hemophilia A Treated with Rurioctocog Alfa Pegol: Final Results from a Prospective Phase 3 Study (ISTH 2026, PB1432)

S. Tangada et al

Background: A phase 3 prospective, uncontrolled, open-label study (NCT02615691) investigated the efficacy and safety of rurioctocog alfa pegol (rAHF-PEG; Adynovate; Baxalta US Inc., a Takeda company, Lexington, MA, USA) in previously untreated patients (PUPs) with severe hemophilia A (HA).

Aims: To evaluate the potential of rAHF-PEG to induce factor VIII (FVIII) inhibitors as well as IgM and IgG antibodies against FVIII, polyethylene glycol (PEG), and PEG-FVIII from this phase 3 study.

Methods: Eligibility criteria encompassed severe HA (FVIII <1%), age <6 years, and <3 exposure days (EDs) to rAHFPEG, octocog alfa, or plasma transfusion. Participants received rAHF-PEG on demand (10–50 IU/kg, up to 80 IU/kg by bleed severity) or prophylactically (≥1×/week, 25–50 IU/kg, up to 80 IU/kg at investigator discretion) for ≥100 EDs or until FVIII inhibitor development (≥0.6 BU/mL). FVIII inhibitors were assessed using the Nijmegen modification of the Bethesda assay. Specificity of binding antibodies with titers ≥1:80 was confirmed by antigen competition using enzyme-linked immunosorbent assay. Ethics committee approval was obtained, and all participants/legally authorized representatives provided informed consent. Data presented from the last participant's last visit (29 October 2024).

Results: Among 146 screened participants, 120 were dosed with rAHF-PEG. Eleven participants developed FVIII inhibitors: five low titer (≥0.6–5 BU/mL) and six high titer (>5 BU/mL). Of the 120 participants, 92 without inhibitors with ≥100 rAHF-PEG EDs were analyzed for binding antibodies. Fifty participants without inhibitors with ≥100 rAHF-PEG EDs tested positive for IgM and/or IgG antibodies, of whom 18 were positive for >1 antibody species. Pre-existing (at screening/baseline) IgM/IgG antibodies were detected in 23 participants; 22 had persistent IgM/IgG antibodies; 33 had transient IgM/IgG antibodies. PEG-FVIII IgGantibodies were most frequently detected

Conclusions: Despite the development of binding antibodies in some PUPs with severe HA receiving rAHF-PEG, the FVIII inhibitor rate remained low. Notably, PEG-FVIII IgG antibodies were observed in 47 participants without inhibitors, despite fewer participants developing FVIII or PEG IgG antibodies.

Bispecific Monoclonal Antibodies (including FVIII Mimetics)

Emicizumab (Hemlibra®)

MRI-Based Assessment of Joint Outcomes in Children With Severe Hemophilia A on Emicizumab Prophylaxis: A Prospective Observational Study (EAHAD 2026, OR02)

L. M. Sherief et al

Introduction: Children with severe haemophilia A experience recurrent joint bleeds leading to long-term arthropathies and impaired quality of life. Emicizumab is the first bispecific monoclonal antibody that was approved for routine prophylaxis in children with haemophilia A. While most studies focused on clinical outcomes, this study evaluated the real-world effectiveness of Emicizumab in improving structural outcomes using MRI-based evaluation and clinical scoring.

Methods: This prospective, observational, multi-center study included male children (<18 years) diagnosed with severe hemophilia A, who received Emicizumab prophylaxis. Each patient underwent clinical and MRI evaluation of the index joints at baseline and after 12 months. Clinical assessments included changes in annual bleeding rate (ABR), Hemophilia Joint Health Score (HJHS), and MRI scores using the International Prophylaxis Study Group (IPSG) version 1.0 scale.

Results: This study included 39 children with severe hemophilia A with a median age of 8 years (range: 4-17years). A total of 54 joints were assessed, including 33knees, 12 ankles, and 9elbows. After one year of Emicizumab prophylaxis, patients showed marked clinical and radiological improvements. The mean ABR significantly decreased from 50 to 0.46 (p<0.001), and the mean HJHS improved from 13 to 8 (p<0.001). Baseline MRI evaluation revealed joint effusions in 100% of joints, with 50.0%, 22.2%, and 27.8% having small, moderate, and large effusions, respectively. After one year, moderate joint effusions were significantly reduced to 11.1%, and none had large effusions. Synovial hypertrophy decreased from 83.3% to 61.1%, and haemosiderin deposition decreased from 66.7% to 16.7% (p<0.001). Osteochondral changes, improved in 22.2% of joints, while only 5.6% showed progression. Almost 88.9% of joints demonstrated improvement on MRI, with 11.1% remaining stable after one year of prophylaxis.

Discussion/Conclusion: Emicizumab prophylaxis resulted in both clinical and radiological improvements in children with severe haemophilia A. These findings support the role of Emicizumab in controlling joint disease progression and improving long-term musculoskeletal outcomes in children with severe hemophilia A.

Inhibitor development during emicizumab prophylaxis in previously treated patients with severe hemophilia A (less than 50 exposure days) (ISTH 2026, OC 35.4)

V. Labarque et al

Background: Inhibitor development is a major complication of Factor VIII (FVIII) replacement therapy in severe hemophilia A (sHA), particularly during the first 50 exposure days (EDs). Although emicizumab prophylaxis has substantially reduced the need for clotting factor concentrate (CFC), FVIII infusions are required for breakthrough bleeding, surgery and trauma. Consequently, inhibitor

development remains possible. Whether the risk and timing of inhibitor development in the emicizumab era differ from the past remains unclear.

Aims: To analyze inhibitor development following emicizumab initiation in patients with sHA (≥ 6 EDs and < 50 EDs) and no history of inhibitors.

Methods: Data on CFC EDs, inhibitor development and established risk factors were extracted from the international Pediatric Network on Hemophilia Management Registry (PedNet) for previously treated patients (≥ 6 EDs and < 50 EDs) on emicizumab (January 1, 2025). Inhibitors were considered clinically relevant if at least two consecutive measurements were positive.

Results: Out of 1625 patients with sHA and no history of inhibitors after ≥ 6 EDs, 331 had started emicizumab prophylaxis. Forty-nine patients had < 50 EDs at initiation of emicizumab (median EDs 14; IQR 8-21). The median observation time was 2.2 years (IQR 1.3-3.2). Six patients received ongoing regular FVIII infusions (1/week to 1/month). Of note, only 6/49 patients had reached 50 EDs at the time of data extraction. Five of these 49 patients (10%) developed an inhibitor before reaching 30 EDs of FVIII (9, 15, 19, 21, and 28 EDs). All 5 patients had a high risk genotype (intron 22 inversion: n=4; large structural change: n=1). Their median EDs before emicizumab was 9 (IQR 7-13). None of them received FVIII regularly while on emicizumab. The median EDs following initiation of emicizumab in these 5 patients was 11 (IQR 4-13); the median time on emicizumab was 1 year (IQR 0.4-2.7). The median peak inhibitor titer was 2.5 (IQR 1.25- 14.3) Bethesda Units.

Conclusions: Even in the era of emicizumab, inhibitor development remains an important complication in sHA, underscoring the ongoing importance of inhibitor testing. However, the true magnitude of this risk has yet to be determined as many patients have not had enough FVIII EDs.

Pharmacokinetic and Pharmacodynamic Variability of Emicizumab in Real-World Haemophilia A Patients: Insights From a Long-Term Single-Centre Cohort Study (WFH 2026, FP-031 (482)

A. Colombo et al

Introduction and Objective: Emicizumab has provided people with haemophilia A (PwHA) stable bleed protection across inhibitor status and age groups. Nevertheless, a subset of individuals continues to experience bleeding despite apparently adequate treatment exposure. This study aimed to evaluate pharmacokinetic and pharmacodynamic variability of emicizumab in a real-word setting.

Materials and Methods: PwHA receiving emicizumab prophylaxis regularly followed up at our Haemophilia Centre were analysed. Plasma samples were collected during follow-up visits irrespective of the interval elapsed since the last emicizumab injection. Emicizumab concentration in plasma and FVIII-like activity by chromogenic assay with human reagents (Biophen FVIII:C, Hyphen BioMed) were measured. Clinical data included number and type of bleeding events.

Results: Forty PwHA (97.5% severe; 40% with current inhibitors; 30% aged < 12 years) received emicizumab prophylaxis for a median of 5.7 years (IQR: 4.4-7.6). During follow-up, 12 patients (30%) were bleed-free, and 28 patients experienced 118 bleeding episodes (81, 69% joint bleeds; 77, 65% spontaneous—Figure 1) treated with either FVIII concentrates or rFVIIa. Blood samples to measure plasma concentrations of emicizumab and FVIII-like activity were drawn after a median of 5 days since the last emicizumab administration (IQR: 2-7; range: 1-21). The median emicizumab concentration was 49 ug/mL (IQR: 43-59) and the median FVIII-like activity of 19.6 IU/dL (IQR: 16-24). There was no correlation between emicizumab concentration, and the time interval elapsed since last administration; while there was a significant correlation between emicizumab

concentration and FVIII-like activity measured with human-based chromogenic assay (r2: 0.81, p < 0.001). The median emicizumab plasma concentration and the median FVIII-like activity were similar between bleeders and non bleeders (47 vs 50.6 ug/ml and 20 vs 19.9 IU/dL, respectively).

Conclusions: In this cohort of patients followed-up for a median of 6 years, emicizumab concentrations in plasma were consistently in the therapeutic range with a FVIII-like activity well beyond 15 IU/dL. At variance with what was expected based on laboratory results, only 30% of patients had no bleeding episodes. This observation indicates that emicizumab concentration and/or FVIII-like activity levels do not reflect the hemostatic potential of the drug and cannot be used to inform levels of protection against bleeds.

NXT007

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)

M. E. Mancuso et al

Background: NXT007, a next-generation bispecific antibody based on emicizumab that mimics activated factor (F)VIII function in people with hemophilia A (HA), was investigated in two Phase I/II, open-label, nonrandomized, multicenter, multiple-ascending-dose (MAD) studies: one in Asia (NXTAGE Part B; jRCT2080224835), one Global (NCT05987449).

Aims: Report outcomes in three pooled NXT007 dose cohorts from two MAD studies (F. Hoffmann-La Roche Ltd/Chugai Pharmaceutical Co., Ltd) with equivalent dosing.

Methods: Eligible participants were emicizumab-naïve and aged 12–64 years (Global study: ≤59 years). Subcutaneous NXT007 maintenance doses in NXTAGE cohorts B2, B3 and B4 are identical to Global cohorts 1, 2 and 3 (0.28, 0.70, and 1.08mg/kg, respectively, every 4 weeks; predicted to achieve nonhemophilic FVIII activity), and are pooled into Groups X, Y, and Z. Loading doses were weekly in NXTAGE Group X and Y (X: six doses; Y: four doses) and as two doses at 2-week intervals in the Global study and NXTAGE Group Z. Informed consent and ethics approval were obtained. Outcomes included safety, pharmacokinetics, pharmacodynamics, immunogenicity, and model-based annualized bleeding rates (ABRs).

Results: Overall, 42 participants received NXT007 (Group X: n=13; Group Y: n=15; Group Z: n=14). Forty (95.2%) had severe HA; one (2.4%; Global study) had FVIII inhibitors. Median (range) age was 36 (12–56) years. At cut-off (NXTAGE: 06-Nov-24; Global: 21-Apr-25), median (range) observation periods in Groups X, Y, and Z were 80.0 (61.1–113.3), 44.1 (42.1–72.4), and 21.6 (5.4–34.4) weeks, respectively. NXT007 had favorable safety outcomes across doses. D-dimer remained within normal range and prothrombin fragment 1+2 elevated slightly; neither increased dose-dependently. ABR (95% confidence interval) for treated bleeds in the maintenance period was 0.3 (0.1–0.8); 36/42 (85.7%) participants had zero treated bleeds. NXT007 plasma concentrations increased dose-dependently, with no ethnic differences. Thrombin generation peak height increased from baseline with all doses. Overall, 34/42 (81.0%) participants developed anti-drug antibodies (ADAs); one (2.4%; Group Y, NXTAGE) had ADAs impacting pharmacokinetics; none impacted safety or cross-reacted with emicizumab.

Conclusions: NXT007 had favorable safety outcomes, with low treated ABRs. One participant had ADAs impacting pharmacokinetics. These data support progression to Phase III trials.

Major Surgeries in People with Hemophilia A under NXT007 Prophylaxis: Experience from NXTAGE Phase I/II Study(ISTH 2026, OC 02.3)

K. Nogami et al

Background: NXT007 is an investigational, next-generation, bispecific antibody, based on emicizumab and optimized to provide increased activated FVIII-mimetic activity. In Parts B and C of a phase I/II study (NXTAGE; jRCT2080224835; for emicizumab-naïve people with hemophilia A (PwHA) without inhibitors and emicizumab-treated PwHA with or without inhibitors, respectively), no treated bleeds were reported in the highest 2 dose cohorts, suggesting the potential to achieve hemostatic normalization. However, it remains unclear whether major surgeries can be successfully accomplished under minimal additional perioperative management.

Aims: To report a first case series in which invasive major surgery was performed with no or minimal doses of additional coagulation factor products in PwHA under NXT007 prophylaxis.

Methods: This report retrieved data on PwHA in NXTAGE receiving NXT007 at 0.7 and 1.08 mg/kg once-every-fourweeks (Q4W) (predicted trough levels of FVIII-equivalent activity at steady state: 73.8 and 93.1 IU/dL, respectively) as maintenance dose who required major surgery. NXTAGE was approved by institutional review boards, and all participants provided written informed consent.

Results: Three patients with severe hemophilia A underwent major surgery and all were on maintenance dose of NXT007 at 1.08 mg/kg Q4W. Patient1: 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. Patient2: A 52-year old non-inhibitor patient underwent total elbow arthroplasty for ulnar nerve disorder. Single dose of 1,000 IU (12.7 IU/kg) standard-half-life FVIII was administered preoperatively on surgery day. Patient3: 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.

Conclusions: 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

Mim8

Mim8 (denecimig) prophylaxis in adults and adolescents with haemophilia A with or without inhibitors: Interim results from the FRONTIER4 long-term safety and efficacy study (ISTH 2026, OC 02.4)

J. Windyga et al

Background: Denecimig (Mim8) is a next-generation, activated factor VIII mimetic intended for subcutaneous prophylaxis of haemophilia A with or without factor VIII inhibitors (HAwI/HA). Previous FRONTIER studies found denecimig efficacious, well-tolerated and without safety concerns.

Aims: To investigate long-term safety and efficacy across denecimig dosing frequencies in adolescents and adults with HAwI/HA.

Methods: The ongoing FRONTIER4 (NCT05685238) extension study enrolled participants from completed denecimig phase 2 and 3 studies. Participants aged ≥12 years received denecimig once-every-week (QW), once-every-two-weeks (Q2W) or once-every-month (QM). Primary endpoints were the number of adverse events (AEs). Supportive secondary endpoints included injection site reactions (ISRs), anti-denecimig antibodies and treated bleeding episodes. Bleeds were analysed using a negative binomial regression model. The study was approved by relevant local ethics committees and participants provided written informed consent.

Results: Of 365 adult/adolescent participants, 24.4% were aged 12-17 years, 11.0% had HAwI and 87.1% had severe haemophilia. Mean (SD) age was 33 (16) years and 98.6% were male. Over a mean treatment analysis period of 0.57 years, no thromboembolic events were reported. Of the serious AEs, 1 fatal outcome was unlikely related to denecimig. Of 6138 injections, only 1.8% resulted in 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. Across QW, Q2W and QM, estimated mean annualised bleed rates (ABRs [95%CI]) were 0.91 (0.66-1.27), 0.55 (0.34-0.87) and 0.74 (0.54-1.02), respectively, and proportions of participants with zero treated-bleed rates were 70.4%, 80.8% and 70.9%, respectively. ABRs across bleed subtypes were low and most participants had zero treated bleeds (Figure 1). ABRs (95%CI) for HA and HAwI participants were 0.88 (0.71-1.08) and 0.15 (0.05-0.45), respectively, across dosing frequencies.

Conclusions: Interim analyses from FRONTIER4 supports long-term safety and efficacy of denecimig prophylaxis in adults and adolescents with consistently low ABRs across flexible dosing frequencies and inhibitor status. Novo Nordisk A/S funded this study.

Mim8 prophylaxis in Children With Haemophilia A: 52-week Efficacy and Safety Outcomes From FRONTIER3 (EAHAD 2026, OR09)

G. Kenet et al

Introduction: Mim8 (denecimig) is a next-generation activated factor VIII mimetic bispecific antibody in development for subcutaneous (SC) prophylaxis in patients with haemophilia A (HA) with (HAwI) or without inhibitors. We report results from the phase 3, open-label FRONTIER3 paediatric study (NCT05306418) at the end of Part 2.

Methods: FRONTIER3 enrolled patients aged 1-11 years with HA (any severity). In Part 1 (26 weeks) patients received SC Mim8 once-every-week (QW). In Part 2 (26 weeks), patients/caregivers chose to remain on QW or switch to once-every-month (QM). Primary endpoint: number of treatment-emergent adverse events (TEAEs). Secondary endpoints included treated bleeds, bleed subtypes, anti-drug antibodies (ADAs) and injection site reactions (ISRs). Mean annualised bleeding rate (ABR) and 95% confidence intervals (CI) were estimated using a negative binomial model.

Results: Of 70 patients completing Part 1, 32 (45.7%) switched to QM in Part 2 (38 [54.3%] remained on QW). Most (60/70, 85.7%) had severe HA; few (14/70, 20.0%) had HAwI (7 on QW; 7 on QM in Part 2). Over 52 weeks, 184 TEAEs were reported in 54 (77.1%) QW patients (total exposure time [TET]: 54.6 years), and 47 TEAs in 20 (62.5%) QM patients (TET: 16.1 years). None were severe; no thromboembolic events or hypersensitivity reactions occurred. ISRs occurred in 7 (10.0%) QW patients (26/2885 injections; 0.9%) and 1 (3.1%) QM patient (5/194 injections; 2.6%). Of 5 (7.1%) patients with anti-Mim8 antibodies, none showed clinical evidence of neutralising ADAs. Estimated mean ABR (95% CI) for treated bleeds with QW was 0.53 (0.30;0.94) in Part 1; 74.3% of patients had zero treated bleeds. In Part 2, estimated mean ABR was 0.42 (0.18;1.00) with QW and 0.25 (0.09;0.66) with QM; 81.6% of QW and 87.5% of QM patients had zero treated bleeds. Estimated

mean ABR for all QW patients during Part 1 and Part 2 was 0.50 (0.30;0.85). Over 52 weeks, no HAWI patients reported treated bleeds. Of 39 treated bleeds, 6 were spontaneous (4 in Part 1 QW, 1 in Part 2 QW, 1 in Part 2 QM). All 10 target joints in 8 (11.4%) patients at baseline were resolved by Week 52.

Discussion/Conclusion: Over 52 weeks, Mim8 QW and QM was well tolerated and provided robust bleed protection in children with HA. All FRONTIER3 completers chose to transfer to the open-label extension, FRONTIER4 (NCT05685238).

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)

M. Carcao et al

Background: Denecimig (Mim8) is a next-generation, activated factor VIII mimetic intended for subcutaneous prophylaxis of haemophilia A with/without factor VIII inhibitors (HAwI/HA). The FRONTIER3 (NCT05306418) phase 3 study found denecimig efficacious, well-tolerated and without safety concerns in children aged 1–11 years with HAwI/HA.

Aims: Follow-up safety and efficacy evaluation of denecimig once-every-week (QW)/once-every-month (QM) and assessment of once-every-two-weeks (Q2W) in children continuing in the FRONTIER4 (NCT05685238) long-term extension study.

Methods: The ongoing FRONTIER4 study enrolled participants including children completing FRONTIER3, who then continued denecimig QW/QM or started Q2W dosing. Number of adverse events (AEs, primary endpoint) and secondary endpoints including injection site reactions (ISRs), anti-denecimig antibodies and treated bleeding episodes (analysed using a negative binomial regression model) were assessed. The study was approved by relevant local ethics committees and appropriate written informed consent was ensured.

Results: Of 61 male children included, 77.0% had HA (23.0% had HAwI), 90.2% had severe haemophilia and mean (SD) age was 6 (3) years. There were no thromboembolic events or hypersensitivity reactions. Of 839 injections, only 2.0% resulted in 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 [95%CI]) were low across dosing frequencies (0.50 [0.21-1.22] and 0.37 [0.10-1.34] for QW and QM, respectively, whilst 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. Across dosing frequencies, estimated mean ABR (95%CI) and median ABR for treated bleeds was 0.37 (0.17-0.76) and 0, respectively, with consistently low ABRs across bleed subtypes. Estimated mean ABRs (95%CI) in HA and HAwI participants were 0.42 (0.16-1.09) and 0.20 (0.02-1.72), respectively.

Conclusions: These interim results align with FRONTIER3 data, further supporting safety and efficacy of denecimig prophylaxis in children, who continued in a long-term extension study, irrespective of inhibitor status and dosing frequency.

INNO8

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

L. Ingemann et al

Background: Inno8 is a bispecific heavy-chain-only antibody fragment that mimics activated factor VIII and is being developed as an oral prophylaxis for hemophilia A. To enable oral bioavailability, Inno8 is formulated as a tablet with salcaprozate sodium (SNAC), an absorption enhancer that facilitates gastric epithelial uptake.

Aims: To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Inno8 in healthy participants.

Methods: VOYAGER1 (NCT06649630) was a randomized, placebo-controlled, first-in-human phase 1 study with single ascending dose (SAD) and multiple ascending dose (MAD) parts in healthy male participants. In the SAD part, 5 cohorts (n=8 each) were randomized to receive a single intravenous infusion of Inno8 (n=6 per cohort) at ascending dose levels or placebo (n=2 per cohort). In the MAD part, 3 cohorts (n=13 each) were randomized to receive once-daily oral Inno8 (n=10) at ascending dose levels or placebo (n=3) for 10 consecutive days. The primary endpoint was the number of treatment-emergent adverse events (TEAEs). Secondary endpoints included maximum observed plasma concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-inf) in the SAD part, and AUC over the 24-hour dosing interval (AUC0-24h) in the MAD part. PD assessments included change from baseline in activated partial thromboplastin time (aPTT) and maximum thrombin generation. VOYAGER1 was approved by an independent ethics committee. Participants' informed consent was obtained.

Results: No serious or severe TEAEs were reported, and no anti-drug antibodies were detected. In the SAD part, PK was dose proportional, with slope estimates of 1.07 (95% CI, 1.03–1.12) for Cmax and 1.09 (95% CI, 0.99–1.19) for AUC0-inf. In the MAD part, slope estimates were 0.98 (95% CI, 0.74–1.22) for Cmax and 0.97 (95% CI, 0.73–1.21) for AUC0-24h, consistent with dose-proportional exposure. Dose-dependent changes in aPTT and thrombin peak height were observed across the dose range for intravenous and oral administration of Inno8.

Conclusions: Inno8 was safe and well tolerated across all tested intravenous and oral dose levels. The doseproportional PK and dose-dependent PD effects support further clinical development of Inno8 as an oral prophylaxis for hemophilia A. This study was sponsored by Novo Nordisk.

Gene Therapy

Valoctocogene Roxaparvovec (Roctavian®)

Characterization of ALT Elevations During the 5-Year GENEr8-1 Trial of Valoctocogene Roxaparvovec Gene Transfer for Severe Hemophilia A (EAHAD 2026, OR16)

R. Klamroth et al

Introduction: Valoctocogene roxaparvovec, the first approved gene therapy for severe HA (FVIII <1 IU/dL), uses an AAV5 vector to deliver a FVIII cDNA to enable FVIII production in hepatocytes to provide bleed protection. The open-label, phase 3 GENEr8-1 trial (NCT03370913) investigated safety and efficacy of valoctocogene roxaparvovec in 134 participants with severe HA. The most common adverse event was asymptomatic transient alanine aminotransferase (ALT) elevation, hypothesized to result from immune-mediated damage to transduced hepatocytes. Here, we characterize ALT elevations from central laboratory data during the 5-year trial.

Methods: Adult male participants with severe HA without history of significant liver dysfunction received an infusion of 6x1013 vg/kg valoctocogene roxaparvovec. ALT was monitored throughout the trial. Reactive glucocorticoids (GCs) were used for ALT elevation at the investigator's discretion. Central lab- reported ALT elevation was defined for all participants as ALT >43U/L(upperlimitofnormal[ULN]).Numberofparticipantswith elevations, number of distinct elevation events per year (onset), severity, and GC use for ALT elevations are reported.Duration of an elevation was considered from onset >ULN to next measurement < ULN.

Results: At baseline, 14.9% and 30.6% of participants had history of hepatitis B and C. The number and severity of ALT elevations were highest in year (Y)1 after gene transfer with 297 elevations in 105/134 (78.4%) participants; all 105 participants received GCs. Subsequently, the number of ALT elevations and participants with elevations decreased and stabilized (Y2, 48 events in 39/134 [29.1%] participants; Y3, 24 events in 20/130 [15.4%] participants; Y4, 27 events in 21/131 [16.0%] participants; Y5, 27 events in 23/129 [17.8%] participants). In Y2, 45/134 (33.6%) participants initiated GCs; 0 did in Y3-5. Over 5 years, 65.0% of ALT elevations were >1-1.5x ULN, 18.6% were >1.5-2x, 10.0% were >2-3x, 3.9% were >3-5x, and 2.6% >5x ULN. After Y2, O elevations >5x ULN occurred. Most elevations were transient. Potential confounding factors contributing to ALT elevation will be presented.

Discussion/Conclusion: In 5 years post-gene transfer, ALT elevations were generally transient and mild, peaking in Y1 before lessening and stabilizing. These data help inform the understanding of the valoctocogene roxaparvovec safety profile.

Vastly Improved Hepatic AAV Gene Therapy for Hemophilia A Using Engineered Factor VIII Combination Variants with Minor Amino Acid Changes (ISTH 2026, OC 18.4)

R. Herzog et al

Background: Clinical gene therapy for hemophilia A (HA) has revealed multiple limitations of expressing B domain deleted FVIII (BDD) in hepatocytes from AAV vectors, including large vector doses to overcome inefficient FVIII synthesis and secretion, substantial inter-patient variability, hepatotoxicities, and declining FVIII expression, which we found to be multifactorial, involving inflammatory responses, cellular stress, and translational shutdown.

Aims: We sought to engineer superior human FVIII variants featuring few amino acid changes.

Methods: Building on our prior variants F309S (reduced ER stress and aggregation), X5 (5 amino acids replaced with porcine residues for enhanced secretion), R336Q/R562 (“QQ”, for APC resistance), combined with deletion of the SQ linker ("ΔSQ" to eliminate proteolytic cleavage sites), we generated 10 (codonoptimized) variants. These were initially compared in C57BL6/129 HA mice (1.0E+11vg/mouse, AAV8 vector with transthyretin promoter, intravenous delivery, 2-week timepoint). Longer-term expression was studied in other HA strains (BALB/c, which are prone to unstable FVIII expression, and C57BL/6), using reduced doses (</=2.0+10 vg). Transient B cell depletion was employed in the inhibitor-prone BALB/c strain. Primary human hepatocytes (PHH) cultures were transduced for mechanistic studies.

Results: Single variants modestly improved expression, with X5 performing best. F309S-X5, ΔSQ-F309S-X5, and all X5-QQ combinations expressed highest (6-9-fold improvement over BDD-WT). In BALB/c HA mice, ΔSQF309S-X5 expressed stably in the normal range (87±30% of normal over 6 months, 6-fold higher than BDD-WT), showing better durability than X5 alone or F309S-X5. Surprisingly, all X5-QQ combinations stably expressed superphysiological levels. In HA C57BL/6 mice, expression of ΔSQ-F309S-X5 was stable at 100-130% with low variability for at least 4 months without immune modulation using 5.0E+9 vg, a 10- fold advantage over BDD-WT. In transgenic mice tolerant to BDD-WT, ΔSQ-F309S-X5 expression was similarly maintained without inhibitor formation. In PHH, ΔSQ-F309S-X5 variant was more efficiently synthesized, more highly secreted, and less aggregated than BDD-WT, with lower induction of the cellular UPR activation marker BiP.

Conclusions: ΔSQ-F309S-X5 is a strong translational candidate for substantially improved HA gene therapy, while interpatient variability and thrombotic risks may complicate use of X5-QQ "super" variants.

BS7189-HSA

A Novel AAV-Mediated Gene Therapy for Hemophilia A Using a FVIII-Mimetic Trispecific VHH antibody (ISTH 2026, OC 18.1)

R. Liu et al

Background: Adeno-associated virus (AAV)-based gene therapy is a transformative approach for hemophilia A (HA), designed to correct factor VIII (FVIII) deficiency through a single intravenous dose of a hepatocyte targeted functional gene vector. However, key challenges remain: the large size of the FVIII transgene exceeds AAV packaging capacity, high vector doses carry risks of hepatotoxicity, transgene expression is often not durable, and conventional treatments are ineffective in patients with neutralizing FVIII inhibitors.

Aims: To address these limitations, we developed a liver-targeted AAV gene therapy encoding a compact and potent FVIII-mimetic heavy-chain variable domain (VHH) antibody, aiming to restore hemostasis irrespective of inhibitor status.

Methods: We engineered BS7189-HSA with a molecular weight of only 38 kDa, a single-chain trispecific antibody composed of three VHHs: one targeting activated factor IX (FIXa), one targeting factor X (FX), and one binding human serum albumin (HSA) to extend half-life. Its hemostatic activity was evaluated in vitro using activated partial thromboplastin time (aPTT) and thrombin generation assay (TGA), and in vivo through blood loss measurements in FVIII-deficient mice and acquired HA models in non-human primates (NHPs). BS7189-HSA was packaged into AAV8 vectors under the control of a liver-specific thyroxine-binding globulin (TBG) promoter, and its plasma levels were quantified by ELISA.

Results: BS7189-HSA restored thrombin generation in FVIII-deficient plasma in a dose-dependent manner, showing ~10-fold higher potency than emicizumab-SIA. Repeated subcutaneous administration of BS7189-HSA (13 doses of 0.5 mg/kg) in NHPs elicited no anti-drug antibodies and caused no observable adverse effects, supporting its low immunogenicity and favorable safety profile. In mice, a single intravenous dose of AAV8-TBG-BS7189-HSA (1.5×10^{11} vg/kg) resulted in sustained serum levels (5-10 μg/mL, well above the coagulation correction thresholds) for at least 24 weeks. Similarly, NHPs receiving AAV8-TBG-BS7189-HSA at 5×10^{12} vg/kg exhibited robust and persistent expression without evidence of hepatotoxicity, cytokine elevation, or other treatment-related pathology.

Conclusions: Liver-directed AAV delivery of the FVIII-mimetic trispecific VHH antibody presents a promising nextgeneration therapy for HA. This approach circumvents the limitations of FVIII gene transfer, enables durable hemostatic correction, and is effective in patients with or without FVIII inhibitors.

Haemophilia B

Factor Replacement Therapies

Eftrenonacog alfa (Alprolix®)

Final Surgery Data from B-MORE: A 24-Month, Prospective, Non-Interventional Study of the Real-World Effectiveness and Usage of rFIXFc in Haemophilia B (ISTH 2026, PB2117)

H. Glosli et al

Background: Extended half-life recombinant factor IX Fc fusion protein (rFIXFc) has established efficacy and safety profiles in people with haemophilia B (PwHB) across surgeries in Phase 3 trials. Real-world data can guide perioperative management.

Aims: To report final surgical data from B-MORE (NCT03901755), a 24-month, prospective, non-interventional, real-world study of rFIXFc effectiveness and usage across Europe/Middle East.

Methods: Analysed PwHB had ≥1 surgery whilst receiving rFIXFc during retrospective/prospective periods. Major surgeries involved general anaesthesia and/or respiratory assistance with a major body cavity penetrated/exposed; other invasive surgeries were minor. rFIXFc usage data reflect surgeries with bolus injections; haemostatic efficacy outcomes also include surgeries with continuous infusion when available. Patients provided informed consent; B-MORE was approved by an independent ethics committee.

Results: B-MORE enrolled 151 PwHB; 32 PwHB underwent 52 surgeries (Table 1). Forty-six surgeries were with bolus injections (9 major, 37 minor), 2 surgeries with continuous infusion (1 major, 1 minor) and 4 minor surgeries with regular prophylaxis. Ten surgeries were major (5 orthopaedic, 5 non-orthopaedic; n=9 PwHB). Median (interquartile range; IQR) rFIXFc consumption from pre-operative loading dose to 24- and 72-hours post-surgery was 134.2 (111.1–182.0) IU/kg with 3.0 (2–3) injections and 227.1 (155.6–266.7) IU/kg with 5.0 (3–5) injections, respectively (n=9 surgeries). Haemostatic efficacy was rated excellent/good for 9 major surgeries (n=1 missing). Median (range) hospitalisation duration was 6.0 (2–10) days (n=9 surgeries). Median (range) estimated intra-/post-operative blood loss was 0.0 (0–750) mL (n=7 surgeries). Forty-two surgeries were minor (n=25 PwHB). Median (IQR) rFIXFc consumption from pre-operative loading dose to 24- and 72-hours post-surgery was 66.7 (39.7–96.4) with 1.0 (1–1) injection and 81.7 (42.3–151.3) IU/kg with 1.0 (1–2) injection, respectively (n=37 surgeries). Haemostatic efficacy was excellent/good for 35 minor surgeries (n=1 fair, n=6 missing). Median (range) hospitalisation duration was 2.0 (1–7) days (n=32 surgeries). No blood loss was reported for minor surgeries. No inhibitor development or surgery-related adverse events (serious/leading to treatment discontinuation) were reported.

Conclusions: Real-world B-MORE data confirm perioperative rFIXFc is highly efficacious and well tolerated in PwHB.

Gene Therapy

Dalnacogene Ponparvovec (BBM-H901)

Safety and Efficacy of Dalnacogene Ponparvovec (BBM-H901) in Moderate to Severe Adult Hemophilia B Participants: Long Term Follow-Up Data in an Early Phase Pilot Study (WFH 2026, FP-014 (77)

F. Xue et al

Introduction and Objective: Dalnacogene Ponparvovec (BBM-H901) is a novel adeno-associated virus (AAV) based gene therapy, which comprises an engineered liver-tropic AAV843 capsid and a liver-specific gene expression cassette containing the hyperactive variant of human factor IX (FIX) -R338L (Padua FIX). In 2019, a pilot study (NCT04135300) was conducted to evaluate its safety and efficacy profiles. This abstract is to report the 5 years follow-up data collected by Nov. 2025.

Materials and Methods: This is an open-label, single-arm, single-center clinical trial in adult participants with moderate to severe hemophilia B at the Institute of Hematology & Blood Diseases Hospital (Tianjin, China). Key inclusion criteria include: baseline FIX coagulation activity (FIX:C) ≤ 2 %, no FIX inhibitor, AAV neutralizing antibody ≤ 1:4 and binding antibody ≤ 1:200, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ two times the upper limit of normal (ULN). Key exclusion criteria include: hepatitis B or C virus infection, ALT and AST > two times the ULN and other severe underlying liver diseases. Dalnacogene Ponparvovec was intravenously infused with a single dose of 5 × 1012 vg/kg. Prophylactic oral prednisone was given at a dose of 1 mg/kg/d before gene therapy and tapered off gradually. FIX:C, annual bleeding rate (ABR) and adverse events were measured regularly.

Results: Ten participants were enrolled and dosed with Dalnacogene Ponparvovec from Oct. 2019 to Jan. 2021. The median follow-up duration till Nov. 2025 is 235.5 weeks and three participants have completed 5-year follow-up. During up to 5 years follow-up after gene therapy, FIX:C measured by one-stage Actin-FSL remained stable, with the mean FIX: above 35%. At all patients' latest follow-up, the mean (+ SD) FIX: level was 40.95 (‡ 24.78)%. One participant experienced a decline of FIX:C < 5% at week 130 and exogenous FIX infusion was resumed. 9/10 participants discontinued FIX replacement completely. The median number of target joints decreased from 1.5 to O. No liver toxicity, drug-related adverse events, FIX inhibitors, thrombosis, or malignancies were reported during long-term follow-up.

Conclusions: Dalnacogene Ponparvovec can provide durable bleeding protection for up to 5 years after gene therapy in hemophilia B patients and was generally well tolerated.

Etranacogene dezaparvovec (Hemgenix®)

Durable Bleed Protection for all Bleeding Subtypes and Favorable Safety Over 5 Years (end-of-study) in the Phase 3 HOPE-B Trial for Persons With Severe or Moderately Severe Haemophilia B (EAHAD 2026, OR11)

F. W. G. Leebeek et al

Introduction: Etranacogene Dezaparvovec (CSL222, Hemgenix) is the first and only approved gene therapy for Hemophilia B (HB) in people with and without pre-existing neutralizing antibodies to adeno-associated virus serotype 5 (AAV5). The pivotal HOPE-B trial (NCT03569891) demonstrated superior bleed protection of etranacogene dezaparvovec (an AAV5 vector containing factor IX [FIX] Padua transgene) compared to FIX prophylaxis over 4 years of post-treatment follow-up. This analysis focuses on FIX-treated bleeds over 5 years post-treatment (HOPE-B end-of-study).

Methods: 54 adult male participants with severe or moderately severe HB (FIX ≤2 IU/dL) received etranacogene dezaparvovec following a ≥6-month lead-in period of their usual FIX prophy-laxis. Adjusted annualized bleeding rates (ABR) for FIX-treated bleeds, FIX consumption, and safety up to 5 years post-treatment are reported.

Results: Mean (SD) endogenous FIX activity (IU/dL) was 39.0 (18.7) at month 6 (n = 51) and maintained at 36.1 (15.7) at year 5 (n = 48) post-treatment. Mean adjusted ABR for all FIX-treated bleeds was reduced from 3.61 in the lead-in period to 1.25 (p = 0.0190) during the entire post-dose period and was <1 for each of the 5 years post-treatment (Table 1). A sustained reduction throughout 5 years of follow-up was observed for mean adjusted ABRs in each subtype of FIX-treated bleeds-spontaneous, traumatic, and joint bleeds-(Table 1), and was <0.5 for each of the 5 years post-treatment. FIX consumption (excluding surgery) was reduced by 96%, and 94% of participants remained free of prophylaxis. No long-term hepatotoxicity or AAV-related oncogenicity was observed.

Discussion/Conclusion: Five-year HOPE-B trial follow-up demonstrated lasting efficacy, including a sustained reduction in FIX-treated bleeds, and a favorable safety profile. Consenting HOPE-B participants will be monitored long-term for a total of 15 years post-treatment in the IX-TEND 3003 study (NCT05962398).

Durable efficacy and safety in responders: 5-Year post hoc end-of-study analysis of etranacogene dezaparvovec in the phase 3 HOPE-B trial in patients with severe/moderately severe haemophilia B (ISTH 2026, OC 21.4)

C. Hermans et al

Background: Etranacogene dezaparvovec is a haemophilia B gene therapy comprising an adeno-associated virus serotype 5 (AAV5) vector and a transgene that expresses the highly active factor IX (FIX) Padua variant. The primary endpoint of the pivotal HOPE-B trial was met (non-inferiority of annualised bleeding rates [ABRs] 7–18 months post-infusion versus lead-in [FIX prophylaxis ≥6 months]). Over 5 years posttreatment, no serious treatment-related adverse events, oncogenicity or late hepatotoxicity were reported; two deaths unrelated to treatment occurred.

Aims: To report a post hoc analysis of 5-year end-of-study outcomes in HOPE-B participants who expressed transgene-derived FIX following etranacogene dezaparvovec treatment, and discontinued prophylaxis (responder population).

Methods: HOPE-B was an international study conducted in adult men with severe/moderately severe haemophilia B (FIX ≤2 IU/dL) and was approved by independent ethics committees. All participants provided informed consent. A single intravenous infusion of etranacogene dezaparvovec (2 × 10 13 genome copies/kg) was administered. Post hoc analysis endpoints included endogenous FIX expression, adjusted ABRs and exogenous FIX use.

Results: Overall, 52/54 (96%) enrolled participants responded to treatment; 50/54 completed the study. Of the two participants without response, one had the highest baseline AAV5 neutralising antibody (NAb) titre (3,212.3) and one received ~10% of the planned dose due to an infusion-related reaction. AAV5 NAb titre ranged between <7–678 in the responder set. Mean (±SD) endogenous FIX activity remained stable from Month 6 (39.0 IU/dL [±18.7]; n=51) to Year 5 (36.1 IU/dL [±15.7]; n=48). Adjusted ABRs significantly decreased during Months 7–60 versus lead-in (Figure 1). Exogenous FIX use was reduced by 98% (262,077 IU/year during lead-in versus 5,919 IU/year over Months 7–60; p<0.0001). One participant (2%) returned to continuous FIX prophylaxis at approximately 29 months post-infusion. Etranacogene dezaparvovec had a favourable safety profile (Pipe SW, et al. N Engl J Med. 2026).

Conclusions: Etranacogene dezaparvovec resulted in sustained near-normal endogenous FIX activity, enhanced bleeding reduction, and substantially decreased FIX usage over 5 years post-infusion in responders, and was accompanied by a favourable safety profile. HOPE-B was funded by uniQure and CSL Behring (NCT03569891).

CSL220

Stable Factor IX Expression and Sustained Reductions in Factor IX Use 9 Years After Gene Therapy With CSL220 in Adults With Haemophilia B (EAHAD 2026, OR12)

W. Miesbach et al

Introduction: CSL220 (formerly AMT-060) is an adeno-associated virus serotype 5 (AAV5) vector encoding a codon-optimized wild-type human factor IX (FIX) gene, driven by a liver-specific promoter. The Phase I/II study (NCT02396342) included 10 patients with haemophilia B (FIX ≤2 IU/dL), who received a single infusion of CSL220 (5x10'2 gc/kg [Cohort 1; n = 5] or 2x10'3 gc/kg [Cohort 2; n = 5]) and had a follow-up of 5 years post-treatment. Cohorts 1 and 2 differed in mean age [Cohort 1: 60.2 (15.9); Cohort 2: 38.2 (5.9)] and the extent of haemarthropathy prior to treatment. Nine out of 10 patients ceased FIX prophylaxis post-treatment. Median (range) FIX activities were 6.5 (6.3-6.7) IU/dL in Cohort 1 (n = 2) and 7.2 (3.8-8.3) IU/dL in Cohort 2 (n = 4) at study completion. Durability and safety are key elements for decision-making regarding gene therapy.

Methods: Patients who completed all assessments in the original trial were enrolled in the open-label, Phase I/IIb extension study (NCT05360706). Four of 5 patients from Cohort 1 (including one patient who remained on FIX prophylaxis) and all 5 patients from Cohort 2 enrolled in the extension study. Data currently available is up to 9 years post-treatment. Data presented are without the patient who remained on prophylaxis, therefore Cohort 1: n = 3; Cohort 2: n = 5.

Results: Median (SD) endogenous FIX activity at Year 9 was 5.0 (3.2-5.5) IU/dL in Cohort 1, and 5.7 (2.9-7.0) IU/dL in Cohort 2. Mean (SD) annualized bleeding rate in Year 9 was 3.6 (4.1) and 1.1 (1.3) for

Cohorts 1 and 2, respectively. Mean (SD) annualized spontaneous bleeding rate was 2.3 (3.9) in Cohort 1 and 0.3 (0.7) in Cohort 2. Mean (SD) annualized FIX consumption during Year 9 was 13067 (15416) IU/year in Cohort 1 and 3644 (6090) IU/year in Cohort 2. No new safety events were identified during Year 9, and no patient returned to continuous FIX prophylaxis.

Discussion/Conclusion: This 9-year follow-up after CSL220 administration provides continued evidence for the durability, stability, and safety of FIX expression after AAV5-based gene therapy, particularly at the 2x10'3 gc/kg chosen for application in Phase 3. CSL220 is the precursor of etranacogene dezaparvovec (CSL222), with only one amino acid difference; hence, these findings might be indicative of the effect of CSL222.

Bypassing Agents

Rebalancing Therapies

Concizumab (Alhemo®)

Concizumab prophylaxis in paediatric participants with haemophilia A/B with inhibitors in the phase 3 explorer10 study: Efficacy, safety and PK/PD results from the 32-week cut-off (ISTH 2026, OC 02.1)

S. Šaulytė Trakymienė et al

Background: Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody approved in the US, Europe and other countries for once-daily, subcutaneous prophylaxis for patients aged ≥12 years with haemophilia A/B with or without inhibitors.

Aims: To assess concizumab efficacy and safety in paediatric participants with haemophilia A/B with inhibitors (HAwI/HBwI) at the explorer10 (NCT05135559) 32-week cut-off.

Methods: The explorer10 multi-centre, non-randomised phase 3 study included male paediatric participants (<12 years) who were concizumab-naïve (arm 1), and participants previously treated with concizumab via compassionate use (arm 2). Concizumab-naïve participants received a 1.0 mg/kg concizumab loading dose (Day 1), followed by 0.20 mg/kg daily starting from Day 2, with potential dose adjustment (5– 8 weeks) to 0.15 or 0.25 mg/kg based on concizumab plasma concentration. The primary endpoint was the number of treated spontaneous/traumatic bleeding episodes during concizumab prophylaxis vs their previous on-demand treatment (≥26 weeks; based on historical medical records) in concizumab-naïve participants (arm 1), with cut-off defined as the time point when all participants in arm 1 had completed their week-32 visit (or withdrawn). Safety and pharmacokinetic/pharmacodynamic (PK/PD) parameters were also evaluated. All participants gave informed consent; the study was approved by local ethics committees.

Results: The estimated mean annualised bleeding rate (ABR) and 95% confidence interval (CI) for 24 participants on concizumab prophylaxis was 2.08 (1.27; 3.41) vs 11.51 (7.75; 17.09) for previous on-demand treatment. The ABR ratio was 0.18 (0.11; 0.29; P<0.001) representing 82% reduction in ABR, showing superiority of concizumab prophylaxis over previous on-demand treatment (Table 1). Concizumab plasma concentration remained stable over time and free TFPI plasma levels decreased and remained stable. The geometric mean thrombin peak increased to within the normal range for adults. Concizumab was well tolerated with no safety concerns identified.

Conclusions: In paediatric HAwI/HBwI, concizumab prophylaxis was effective in bleed prevention compared with previous on-demand treatment. The safety profile is consistent with previous observations.

Marstacimab (Hympavzi®)

Health-Related Quality of Life Outcomes for Marstacimab in Participants With Severe Hemophilia A or Moderately Severe to Severe Hemophilia B With Inhibitors: Results From the Phase 3 BASIS Trial (WFH 2026, FP-010 (214))

J. Mahlangu et al

Introduction and Objective: Individuals with hemophilia A (HA) or B (HB) experience substantial disease burden, impaired functioning, and reduced quality of life. This is the first comprehensive assessment of health-related quality of life (HRQOL) and patient-reported outcomes (PROs) in HA/HB participants with inhibitors treated with marstacimab in the BASIS phase 3 trial (NCT03938792).

Materials and Methods: Males aged ≥ 12-< 75 years with severe HA (factor VIII < 1%) or moderately-severe to severe HB (factor IX ≤ 2%) entered a 6-month observational phase (OP) with on-demand (OD) or prophylactic bypassing agents, followed by a 12-month active treatment phase (ATP) with sub-cutaneous marstacimab (300-mg loading, 150-mg once-weekly maintenance dose). Participants completed PRO assessments at baseline and scheduled visits: Haemophilia QoL Questionnaire (Haem-A-QoL; physical health domain and total score), EQ-SD-5L, Hemophilia Activities List v2 (HAL2), Patient Global Impression of Change-Hemophilia Questionnaire (PGIC-H), and Hemophilia Life Impacts Questionnaire (HLIQ). Missing data were imputed using multiple imputation under a missing-at-random assumption (except HLIQ).

Results: Of 60 participants in the OP (median age 23 years), 51 (OD, n = 48; RP, n = 3) received marstacimab in the ATP. The primary efficacy analysis focused on OD participants (n = 48). Marstacimab significantly improved multiple HRQOL measures. Changes in Haem-A-QoL physical health domain and total score and EQ-5D-5L index score exceeded the minimal clinically important difference at 6 months vs baseline (Table 1). Significant improvements were seen in Haem-A-QoL physical health domain ($p < 0.0001$) and total ($p < 0.0001$) scores, EQ-5D-5L index score ($p = 0.0377$), and HAL2 self-perceived functional abilities ($p = 0.0085$), with numerical improvement for EQ-VAS ($p = 0.1184$). PGIC-H: Most OD participants reported their impression of their life greatly improved with marstacimab (Table 2). HLIQ: Improvements were seen in most domains related to life impacts associated with living with and treating haemophilia. HRQOL improvements were also observed in RP participants (no statistical analysis undertaken).

Conclusions: Marstacimab produced clinically relevant and statistically significant improvements in HRQoL, functional status, and patient-perceived benefit in HA/HB participants with inhibitors. Despite limitations related to open-label design, modest sample size, and absence of a concurrent comparator, these findings support the meaningful impact of marstacimab on PROs. Longer-term durability and association with bleed reduction will be evaluated in the open-label extension study.

Joint Health in Participants With Hemophilia A or B With Inhibitors Treated with marstacimab in the Phase 3 BASIS Trial (EAHAD 2026, OR08)

J. Mahlangu et al

Introduction: Patients with hemophilia A (HA) or B (HB) with inhibitors face limited prophylactic options and remain at risk of progressive joint damage. Marstacimab, a human monoclonal antibody targeting tissue factor pathway inhibitor, rebalances hemostasis independently of factor

replacement. We evaluated the impact of marstacimab on joint health in participants (pts) with inhibitors in the BASIS trial (NCT03938792).

Methods: BASIS was an open-label, phase 3 study in males aged ≥12 to <75 years with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%). Pts entered a 6-month observational phase (OP) with on-demand or prophylactic bypassing agents, followed by a 12-month active treatment phase (ATP) with subcutaneous (SC) marstacimab (300 mg loading, 150 mg once-weekly [QW] maintenance). Treated joint bleeds and treated target joint bleeds, target joints (major joints with ≥3 spontaneous bleeds over 6 months) and Hemophilia Joint Health Score (HJHS) were assessed.

Results: Of 60 pts with inhibitors (HA n = 47; HB n = 13; median age 23 years) in the OP, 51 received marstacimab in the ATP. At study entry, 43/60 (71.7%) pts had ≥1 target joint. In the on-demand subgroup (n = 48), model-based mean (descriptive median) annualized bleeding rate (ABR) for treated joint bleeds decreased from 15.15 (11.66) in the OP to 1.10 (0.00) in the ATP (mean ratio 0.07 [95% CI 0.04, 0.14]; P<0.0001). Mean (range) target joints decreased numerically from 0.6 (0.0-4.0) in the OP to 0.0 (0.0-1.0) over 12 months in the ATP. Model-based mean (descriptive median) ABR for treated target joint bleeds declined from 6.42 (2.09) to 0.79 (0.00) (mean ratio 0.12 [95% CI 0.06, 0.25]; P = 0.0001). HJHS improved modestly from baseline; total score was lower after 6 months in the ATP vs 6 months in the OP (median difference, -2.2 [95% CI -5.7, 1.4]; P = 0.2341).

Discussion/Conclusion: In BASIS pts with inhibitors, marstacimab markedly reduced joint and target joint bleeding and eliminated most target joints over 12 months of treatment, with early trends toward improved HJHS. Longer-term improvements in joint health will be assessed during the BASIS open-label extension study. These findings support QW SC marstacimab as a promising prophylactic option for patients with inhibitors at risk of progressive arthropathy.

Marstacimab prophylaxis in pediatric participants with hemophilia A or B with or without inhibitors: interim results from the phase 3 BASIS KIDS trial (ISTH 2026, LB 02.1)

G. Kenet et al

Background: Marstacimab is approved for individuals aged ≥6 years with hemophilia A (HA) or B (HB) with and without inhibitors. Aims To evaluate marstacimab efficacy and safety in pediatric participants with severe HA (FVIII activity <1%) or moderately severe or severe HB (FIX activity ≤2%) with or without inhibitors.

Methods: BASIS KIDS (NCT05611801) is an ongoing open-label, phase 3 study designed to enroll pediatric participants aged ≥1 to <18 years, in sequential manner (≥12-<18 years, ≥6-<12 years, with planned 2026 enrollment for ≥1-<6 years) based on established risk–benefit of the preceding age group. Participants receive a subcutaneous marstacimab loading dose (≥12-<18 years: 300mg; ≥6-<12 years: 150mg) followed by once-weekly dosing (≥12-<18 years: 150mg; ≥6-<12 years: 75mg) for 12 months. Primary endpoints are annualized bleeding rate of treated bleeds (ABRtreated) with marstacimab vs the historical 12-month period prior to consent with on-demand (OD; inhibitor cohort) or routine prophylactic (RP; non-inhibitor cohort) treatment and safety. No hypothesis testing was performed in this non-prespecified interim analysis.

Results: At data cut-off (May 26, 2025), 92 participants (median age: 10.0 years) received marstacimab; 25 (27%) with inhibitors (OD: n=17; RP: n=8), 67 (73%) without inhibitors (RP: n=67) (Table 1). At that time, 54 (58.7%) participants completed the study, 3 (3.3%) discontinued, and 35 (38.0%) were ongoing. Mean estimated (95%CI) ABRtreated (in completers) was 1.44 (0.60-3.44) with marstacimab vs 18.92 (15.22-23.52) with historical OD treatment (estimated ABR ratio: 0.076;

92.4% reduction) for inhibitor participants (n=14) and 1.84 (1.25-2.43) vs 3.55 (1.87-5.23) with historical RP (estimated ABR difference: –1.71; 48.1% reduction) for non-inhibitor participants (n=36) (Table 2). Results were consistent by hemophilia type, age, race, and geographic subgroup. Of all dosed participants, 67 (72.8%) experienced adverse events (AE); 64 (69.6%) experienced mild/moderate AEs, and 2 (2.2%) had serious AEs while on treatment. There were no deaths, thrombotic events, or permanent discontinuations from treatment or the study due to AEs.

Conclusions: 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

Von Willebrand Disease and Other Rare Bleeding Disorders

Vonicog alfa (Veyvondi, Vonvendi®)

Recombinant von Willebrand Factor Prophylaxis for Severe von Willebrand Disease: Final Results Focusing on Adults Receiving Once Weekly Prophylaxis in a Phase 3b Continuation Study (EAHAD 2026, OR14)

S. Susen et al

Introduction: Recombinant von Willebrand factor (rVWF, Takeda Pharmaceuticals U.S.A., Inc.) product labels recommend 40-60 IU/kg prophylaxis twice weekly in adults with von Willebrand disease (VWD); however, an individualized reduced dosing frequency may reduce treatment burden. We present final data for adults (≥18 years) with severe VWD (baseline VWF:ristocetin cofactor <20 IU/dL) who received rVWF prophylaxis in an open-label, prospective, multicenter, Phase 3b continuation study (NCT03879135), focusing on a post hoc analysis of adult participants (pts) who received once weekly (QW) dosing.

Methods: The study enrolled rollover pts from a Phase 3 adult prophylaxis study (NCT02973087) and non-rollover pts who had ≥3 treated spontaneous bleeding events (BEs) and had received on-demand (OD) treatment with VWF products in the prior 12 months (mos). Pts received 1-3 years' rVWF prophylaxis, starting with 50+10 IU/kg (up to 80 IU/kg) 1-3 times weekly, tailored based on pharmacokinetics, BE history and dose in the parent study. The primary endpoint was annualized bleeding rate of treated spontaneous BEs (SABR) over the first 12 mos' rVWF prophylaxis.

Results: Fourteen adult pts enrolled to receive rVWF prophylaxis (rollover n = 11); starting regimens were QW (n = 5), twice weekly (n = 8), or 3 times weekly (n = 1). For the 5 pts on QW dosing (rollover n = 2; non-rollover n = 3), median(range) age was 35.0(25-77) years, 4 pts were White, 2 were female, 4 had Type 2A and 1 had Type 3 VWD. All 5 pts completed the study with 35-36 mos' treatment. Median(range) 12-mo sABR was 1.0(0.00-3.12), similar to all prophylaxis pts (1.0[0.00-7.47]); for the 3 non-rollover pts, sABR reduced compared with their historical SABR while on OD therapy (Table). The 2 rollover pts maintained a similarly low sABR (0 and 0.33) as in the parent prophylaxis study. The mean(SD) weekly dose and number of infusions were 63.8(10.42) IU/kg and 1.1(0.16), respectively. After ~2 years on QW dosing, only 2 pts had their dose escalated to twice weekly for breakthrough BEs. No rVWF-related adverse events, hypersensitivity reactions or thromboembolic events occurred in pts with prophylaxis, and there were no instances of inhibitor development.

Discussion/Conclusion: Once weekly rVWF prophylaxis can be an efficacious treatment option with a favorable safety profile for adults with severe VWD.

HMB-002

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

P. Raheja et al

Background: Von Willebrand disease (VWD) is caused by quantitative or qualitative defects in von Willebrand factor (VWF), a protein essential for primary (platelet adhesion) and secondary (factor VIII stabilization) hemostasis. VWF deficiency leads to recurrent hemorrhagic events across severity levels, often requiring intravenous VWF/FVIII replacement therapy. No subcutaneous prophylactic therapy currently exists. HMB-002 is a subcutaneously administered monovalent antibody designed for prophylaxis in patients with various VWD subtypes. By binding to circulating VWF, HMB-002 elevates both VWF and FVIII levels, addressing the primary and secondary hemostatic defects characteristic of VWD. We present interim results from a first-in-human study of HMB-002 in VWD.

Aims: To evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following a single subcutaneous dose of HMB-002. Methods VELORA Pioneer (NCT06754852) is an ongoing Phase 1/2, open-label, dose-escalation study evaluating HMB-002 in adults with VWD (baseline VWF activity ≤40 IU/dL, FVIII ≤70 IU/dL). The study consists of Part A (single ascending dose) and Part B (multiple dose assessment). Part A evaluated single ascending subcutaneous doses (20, 50, 150 mg) in sequential cohorts.

Results: PD effect was evident from a dose-dependent accumulation of VWF and FVIII. In cohort A2 (50 mg), >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, with stable multimer distribution. PK analysis showed dose-dependent increases in HMB-002 plasma concentrations and prolonged exposure with subcutaneous dosing. 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. Data for cohort A3 (150 mg) are accruing; updated results will be presented at the congress.

Conclusions: 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. These interim results support continued dose escalation to further evaluate PD magnitude and durability.

HMB-003

A long-acting peptide plasmin inhibitor with extended antifibrinolytic activity enabling once-per-cycle subcutaneous treatment for heavy menstrual bleeding: Preclinical development of HMB-003 (ISTH 2026, OC 05.1)

H. Østergaard et al

Background: Heavy menstrual bleeding affects millions of women who lack adequate non-hormonal treatment options. Tranexamic acid (TXA), an inhibitor of tPA-dependent plasminogen activation, provides short-lived antifibrinolytic activity requiring thrice-daily dosing which, together with tolerability challenges, may compromise adherence. To address these limitations, HMB-003 was developed as a long-acting peptide that directly inhibits plasmin at its active site, providing

antifibrinolytic activity independent of the plasminogen activation pathway. Half-life extension is achieved through fatty diacid conjugation, reducing clearance of HMB-003 via reversible albumin binding.

Aims: To evaluate the functional properties, pharmacokinetics (PK), pharmacodynamics (PD), and antifibrinolytic activity of HMB-003.

Methods: Binding affinities were determined using flow-induced dispersion analysis (FIDA). Antifibrinolytic activity was measured using turbidimetry, plasmin generation, and thromboelastography (TEG). Selectivity was evaluated by thrombin generation and platelet aggregometry. PK/PD was determined in Göttingen minipigs following intravenous (IV) or subcutaneous (SC) administration. Antifibrinolytic efficacy was assessed in C57BL/6 mice using intravital fluorescence microscopy to quantify fibrin accumulation at injury sites.

Results: Binding studies revealed sub-nanomolar and low micromolar affinities of HMB-003 for plasmin and albumin, respectively, and confirmed the ability of HMB-003 to simultaneously engage both targets as predicted by molecular modelling. In tPA or uPA-supplemented human plasma or whole blood, HMB-003 demonstrated concentration-dependent inhibition of fibrinolysis with IC_{50} values from 1 to 5 µM. Selectivity was confirmed in human plasma with no effect on thrombin generation or platelet aggregation. In minipigs, HMB-003 reached peak plasma levels within one day after SC administration and displayed a terminal half-life of 153 hours. At an IV dose of 3.3 mg/kg HMB-003, tPA-supplemented minipig plasma exhibited complete inhibition of fibrinolysis for 7 days followed by a gradual return to baseline. In tPA (5 mg/kg)-treated mice subjected to localized electrolytic injury of the femoral vein, HMB003 (1-8 mg/kg) dose-dependently restored fibrin accumulation at the injury site.

Conclusions: HMB-003 demonstrates potent and selective antifibrinolytic activity with a PK/PD profile supporting sustained hemostatic coverage throughout a menstrual period from a single subcutaneous dose. These preclinical data support further development of HMB-003 as a non-hormonal antifibrinolytic therapy that may address limitations associated with current options.

HMB-003, a long-acting peptide plasmin inhibitor, potently inhibits fibrinolysis and localizes with fibrin in a human whole blood microfluidic flow model (ISTH 2026, OC 09.5)

M. Zivkovic et al

Background: HMB-003 is a peptide-based inhibitor of fibrinolysis that acts by directly targeting the active site of plasmin. HMB-003 incorporates a fatty diacid moiety enabling reversible albumin binding and reducing in vivo clearance. In animal models, HMB-003 demonstrates a week-long half-life. This profile positions HMB-003 as a potential once-per-cycle subcutaneous treatment for heavy menstrual bleeding, a condition for which the only non-hormonal treatment, tranexamic acid (TXA), requires multiple daily administrations due to its short half-life, posing challenges for adherence. While antifibrinolytic activity of HMB-003 has been confirmed in static assays and animal models, its effect under physiologically relevant flow conditions in human blood remains to be characterized.

Aims: To evaluate the antifibrinolytic activity of HMB-003 in comparison with TXA in a microfluidic human whole blood-based flow model.

Methods: Platelets and fibrin were fluorescently labeled, and whole blood was recalcified and supplemented with 30 nM tissue plasminogen activator (tPA) and 0-10 µM HMB-003 or 0-240 µM

TXA prior to perfusion over a collagen/tissue factor surface at a shear rate of 300 s^{-1}. Additionally, localization of HMB-003 was assessed using a fluorescently labeled HMB-003 with retained activity. Platelet adhesion, fibrin formation, and HMB-003 localization were visualized using a Zeiss Z1 observer microscope.

Results: Perfusion of whole blood over the collagen/tissue factor surface resulted in platelet adhesion and stable fibrin formation. In tPA supplemented whole blood, fibrin formation was followed by rapid and complete lysis within 5 minutes. HMB-003 inhibited fibrinolysis in a concentration-dependent manner with a mean IC50 [95% CI] of 2 [1-4] µM, demonstrating ~30-fold greater potency than TXA (IC50 67 [26-193] µM). An analog of HMB-003 unable to bind plasmin did not inhibit fibrinolysis, confirming that activity requires direct plasmin engagement. Localization studies demonstrated colocalization of fluorescently labeled HMB-003 with fibrin in the formed clot.

Conclusions: HMB-003 potently inhibits fibrinolysis in a human whole blood microfluidic model that recapitulates key elements of hemostasis under flow. Colocalization with fibrin is consistent with the expected ability of HMB-003 to inhibit both free and fibrin-bound plasmin. Combined with its extended half-life, these findings support continued development of HMB-003 as a novel antifibrinolytic agent for heavy menstrual bleeding.

SR604

Clinical evaluation of SR604, a novel anti–activated protein C antibody, for prophylactic treatment of hemophilia and factor VII deficiency (ISTH 2026, OC 32.4)

R. Yang et al

Background: Activated protein C (APC) specifically downregulates local thrombin generation by inactivating factors Va and VIIIa, a physiological mechanism limiting excessive coagulation at sites of vascular injury. SR604 is a humanized monoclonal antibody that blocks APC without affecting protein C, thereby selectively inhibiting local anticoagulant activity. In preclinical models, SR604 prevented bleeding in hemophilia A/B and other factor deficiencies, supporting its potential as a broad-spectrum hemostatic therapy.

Aims: To evaluate the safety, pharmacokinetics/pharmacodynamics (PK/PD), and prophylactic efficacy of SR604 in patients with hemophilia A or B (with or without inhibitors) and congenital factor VII (FVII) deficiency.

Methods: This open-label, multicenter phase I/IIa trial (ChiCTR2500110665) was conducted in China. Phase I was a single-dose, subcutaneous, dose-escalation study (0.025–0.8 mg/kg; six cohorts; n=16). Phase IIa enrolled 24 patients receiving biweekly subcutaneous prophylaxis for 24 weeks at 0.05 mg/kg (loading 0.1 mg/kg) or 0.1 mg/kg (loading 0.2 mg/kg).

Results: In phase I, SR604 was well tolerated (Table 1). All adverse events were grade 1–2, with no treatment-related events, thrombotic complications, or injection-site reactions. SR604 exhibited linear pharmacokinetics across the tested dose range. Low-titer anti-drug antibodies (ADA) were detected in 6 patients without impact on safety or PK. Bleeding frequency decreased in a dose-dependent manner during post-dose follow-up (Table 2). In phase IIa, SR604 prophylaxis demonstrated an excellent safety profile with no serious adverse events or thrombotic events (Table 1). ADA was detected in two patients, including one case with neutralizing activity. Both dose cohorts showed substantial reductions in total, spontaneous, and joint annualized bleeding rates

compared with pre-treatment baselines (Table 2). One patient with congenital FVII deficiency experienced zero bleeding throughout the 24-week prophylactic period.

Conclusions: SR604 demonstrated excellent safety, linear PK, and significant prophylactic efficacy in patients with hemophilia A or B and congenital FVII deficiency. By selectively neutralizing local APC while preserving systemic anticoagulation, SR604 provides effective hemostasis without detectable thrombotic risk. These results position SR604 as a long-acting and broad-spectrum prophylactic therapy for congenital bleeding disorders. A phase IIb trial (0.4 mg/kg every 4–8 weeks) is ongoing to confirm its long-term efficacy and dosing flexibility.

Sutacimig

Sutacimig Prophylaxis in Glanzmann Thrombasthenia: Results from a Phase 2 Long-Term Extension (ISTH 2026, OC 57.3)

Q. Van Thillo et al

Background: Glanzmann thrombasthenia (GT) is a severe platelet disorder, resulting in impaired platelet aggregation. 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.

Aims: This study evaluates sutacimig as prophylactic therapy for GT.

Methods: This open-label study enrolled adults with GT. Following a 6-week run-in with prospective bleeding event documentation, participants received subcutaneous sutacimig prophylaxis for 12 weeks with option to continue in long-term extension. Four dosing cohorts evaluated: 0.3 mg/kg Q2W (n=11); 0.6 mg/kg Q2W (n=13); 0.9 mg/kg Q2W (n=5); 0.3 mg/kg Q1W (n=5). Primary endpoint was safety; secondary endpoints included PK, PD, and preliminary efficacy measured by annualized treated bleeding rate (ATBR) reduction.

Results: As of October 14, 2025, 34 participants enrolled in the treatment period; 28 continuing in extension. Median age 40.5 years, baseline ATBR 42.0 (95% CI: 23.8, 74.3), median exposure 6.9 months (range 1.9- 15.9). Adverse events were predominantly mild to moderate. Three treatment-related thromboembolic events occurred (all grade 2, with multiple concurrent risk factors, managed with anticoagulation): proximal DVT (at highest dose level), isolated distal DVT, and subsegmental PE. PK and PD analyses demonstrated dose-proportional increases in exposure and accumulation of total FVII(a) and FVIIa with a strong correlation between PK and PD. Three participants underwent procedures: 2 invasive surgeries (skin cancer surgery and partial mastectomy) and 1 dental procedure, all with successful hemostatic outcomes requiring minimal to no intervention; 1 required post-procedure rFVIIa (5 mcg/kg) x 1 dose. Treatment period showed 47% (95% CI: 24%, 63%) ATBR reduction, with clinical activity across dose levels, by bleed location and cause, and with extended treatment beyond 12 weeks. Weekly dosing cohort (n=4) had 87% (95% CI: 80%, 91%) ATBR reduction. Seven participants achieved 100% ATBR reduction. Marked reduction was observed in ATBR of bleeding events treated with high-intensity treatments (rFVIIa, transfusions, procedures).

Conclusions: Safety and clinical activity results continue to support potential of sutacimig as the first prophylactic therapeutic option for GT and will inform optimal dose selection and study design for Phase 3 development.

VGA039

Subcutaneous Four-Week Dosing of the Novel Protein S Antibody VGA039 Demonstrates Safety and Clinically Meaningful Bleed Reduction in Patients With Von Willebrand Disease: Phase 1/2 Multi-Dose Study Results (WFH 2026, FP-006 (389)

J. Mason et al

Introduction and Objective: Von Willebrand disease (VWD) causes recurrent and prolonged bleeding, leading to clinical sequelae and high treatment burden due to the need for frequent infusions. VGA039 is a fully human IgG4 monoclonal antibody that inhibits Protein S cofactor activity, thereby enhancing thrombin generation and promoting primary and secondary hemostasis. In a prior single-ascending-dose study, VGA039 was safe and associated with a reduction in bleeding events.This multi-dose study evaluated the safety, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous (SC) VGA039 prophylaxis in patients with all types of VWD.

Materials and Methods: This open-label, phase 1/2 study (NCT05776069) was conducted in symptomatic participants aged 12-60 years with any type of VWD. Key eligibility criteria included baseline FVIII activity less than the lower limit of normal and no laboratory evidence of thrombophilia or history of thromboembolism. Participants received scheduled doses of SC VGA039 over 120 days with up to 42-day follow up and optional participation in an open-label extension study. Safety, efficacy, pharmacokinetic, and pharmacodynamic parameters were collected.

Results: As of November 14, 2025, a total of 16 participants (aged 15-53 years, weighing 45-160.5 kg) with various VWD types received a single SC loading dose on Day 1, followed by up to 5 SC maintenance doses every 4 weeks starting on Day 8. Six participants in Cohort MD-1 received a flat dose of 225 mg SC VGA039. Ten participants in Cohort MD-2 received weight-banded doses of SC VGA039 per the following criteria: 187.5 mg (45- < 60 kg; n = 0), 262.5 mg (60-100 kg; n = 7), or 450 mg > 100 kg; n = 3). There were no serious drug-related AEs or clinically significant elevations in D-dimer levels. VGA039 achieved plasma concentrations consistent with the anticipated therapeutic range. Efficacy was analyzed in participants (n = 8) who completed the treatment period demonstrating reductions of 41%-100%. All participants completing the study elected to continue in the open-label extension study.

Conclusions: VGA039 administered subcutaneously every four weeks was safe, well tolerated, and associated with clinically meaningful reductions in bleeding across VWD subtypes in this interim analysis. These findings support the ongoing Phase 3 trial (NCT07115004).

Pilot Study Exploring the Lived Experiences of Adolescents and Adults With von Willebrand Disease Treated With VGA039 and Their Families in the VIVID-3 Phase 1/2 Clinical Study (WFH 2026, PP-370 (404)

S. Nataraj et al

Introduction and Objective: Von Willebrand disease (VWD) is characterized by frequent, prolonged, and excessive bleeding that can substantially affect the quality of life of patients and their families. Despite available treatments, many people with VWD continue to experience physical limitations, psychosocial burden, and treatment-related challenges given the standard of care is IV infusions multiple times per week. VGA039 is an investigational, once-monthly subcutaneous monoclonal

antibody that targets Protein S and has dual actions: promoting platelet attachment and enhancing fibrin deposition by increasing thrombin generation to restore hemostasis. The VIVID-3 phase 1/2 trial is designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of VGA039 administered every 4 weeks to patients with any type of VWD over 17 weeks. To complement clinical endpoints, qualitative insights from patients and caregivers are needed to understand the holistic experience with investigational treatments like VGA039 that may address unmet needs of available therapies. This study aims to characterize the lived experiences and quality of life impact of the VWD patient and caregiver before and after treatment with a novel agent, VGA039, during the VIVID-3 study.

Materials and Methods: This is a non-interventional, single-site study of up to three participants from VIVID-3 and one caregiver. Eligible participants are ≥ 12 years, English-speaking, and must have completed the VIVID-3 study or be a family member of a VIVID-3 completer. Participants will complete a ~60-minute web-based semi-structured interview conducted by trained qualitative researchers. All interviews will be audio-recorded, transcribed, and analyzed using MAXQDA software with inductive thematic coding. The study has received IRB approval.

Results: Thematic findings from the interviews will be presented. Anticipated themes include bleeding burden, emotional well-being, physical functioning, social functioning, work or school experience, daily activities, future outlook, overall quality of life, family experiences (caregiver only), and perceptions of treatment.

Conclusions: This qualitative study will provide patient-centered context around a novel, once monthly, subcutaneous therapy, helping to identify domains of impact that are not fully captured by existing clinical trial outcome measures. Early insights into patient and caregiver experiences with VGA039 will be gleaned and will support further research to capture patient-centered outcomes pre- and post-investigational treatments in clinical trials.

Section 4 - Tables

FVIII MIMETICS AND OTHER NON-REPLACEMENT THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Bi-specific monoclonal antibody	Haemophilia A	Mim8	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Novo Nordisk	Phase 3
Bi-specific monoclonal antibody	Haemophilia A	NXT007	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Chugai and Roche	Phase 1/2
Bi-specific monoclonal antibody	Glanzmann Thrombasthenia	HMB-001 (Sutacimig)	Bispecific antibody binding to FVIIa and TLT-1	Subcutaneous	Hemab	Phase 2
Aptamer	Haemophilia A, Type 2B VWD	Rondoroptivon pegol BT200	Pegylated aptamer binding to vWF	Subcutaneous	Medical University of Vienna	Phase 2
Bispecific antibody fragment (oral)	Haemophilia A	Inno8	FVIII mimetic; oral bispecific VHH-based (nanobody) fragment binding FIXa and FX, formulated with the absorption enhancer SNAC	Oral (also IV in early studies)	Novo Nordisk	Phase 1
Monoclonal antibody	Von Willebrand disease	HMB-002	Binds circulating VWF, elevating VWF and FVIII levels	Subcutaneous	Hemab Therapeutics	Phase 1

Monoclonal antibody	Von Willebrand disease	VGA039	Anti-Protein S antibody; attenuates Protein S cofactor function to enhance thrombin generation	Subcutaneous	Star Therapeutics (formerly Vega Therapeutics)	Phase 3 (ongoing); Phase 1/2 completed
Peptide plasmin inhibitor	Heavy menstrual bleeding	HMB-003	Long-acting peptide that directly inhibits plasmin at its active site; half-life extended via fatty diacid conjugation/reversible albumin binding	Subcutaneous	Hemab Therapeutics	Preclinical

REBALANCING THERAPIES (NON-REPLACEMENT THERAPIES) IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
NRT siRNA	Haemophilia A or B w/ or w/o inhibitors	Fitusiran	Antithrombin Small interfering (si)RNA to down-regulate antithrombin	Subcutaneous	Sanofi	Phase 3
NRT Activated Protein C inhibitor	Haemophilia A or B w/ or w/o inhibitors	SerpinPC	Activated Protein C inhibitor	Subcutaneous	Apcintex	Discontinued
Monoclonal antibody Anti-activated Protein C (APC) antibody	Haemophilia A or B w/ or w/o inhibitors, and congenital Factor VII deficiency	SR604	Anti-activated Protein C (APC) antibody	Subcutaneous	Equilibra Bioscience / Shanghai RAAS	Phase 1/2a

GENE THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Gene Therapy	Haemophilia A	PF-07055480 giroctocogene fitelparvovec (formerly SB-525)	Gene therapy using a rAAV2/6 vector, encoding the B-domain deleted human FVIII	Single intravenous infusion	Sangamo	Phase 3
Gene Therapy	Haemophilia A	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Single intravenous infusion	Bayer	Phase 1/2
Gene Therapy	Haemophilia A	Dirloctogene samoparvovec SPK-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Single intravenous infusion	Roche, formerly Spark	Phase 3 trial withdrawn
Gene Therapy	Haemophilia A	AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	Single intravenous infusion	UCL/St. Jude	Phase 1/
Gene Therapy	Haemophilia A	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Single intravenous infusion	Expression Therapeutics	Phase 1
Gene Therapy	Haemophilia A for HAwI	SPK-8016	Recombinant AAV composed of a liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette	Single intravenous infusion	Spark	Refocus on developing an enhanced-function Factor VIII variant
Gene Therapy	Haemophilia A	YUVA-GT-F801	Autologous HSC/MSC modified with lentivirus encoding FVIII	Single intravenous infusion	SGIMI	Phase 1

Gene Therapy	Haemophilia A	-	Non-viral technology using closed-ended DNA (ceDNA) delivered via a cell-targeted lipid nanoparticle (ctLNP) system	-	Generation Bio	Preclinical
Gene Therapy	Haemophilia A	-	in vivo by iv infusion of two components: an AAV vector delivers a promoterless FVIII DNA cassette and a lipid nanoparticle (LNP) delivers a mRNA encoding MG29-1, a Type V CRISPR nuclease and its associated guide RNA	Intravenous infusion	Metagenomi Therapeutics	Preclinical
Gene Therapy	Haemophilia A	ASC618	AAV-8 vector containing a hepatic combinatorial bundle promoter, liver specific codon optimisation, and highly expressing bioengineered human FVIII (ET3) transgene.	Single intravenous infusion	ASC Therapeutics	Phase 1/2
Gene Therapy	Haemophilia A	CD68-ET3-LV-CD34+	CD34+ hematopoietic stem cells transduced with CD68-ET3 lentiviral vector (encoding human factor VIII gene) is administered by IV infusion following conditioning regimen	Single intravenous infusion	Christian Medical College, Vellore, India	Phase 1
Gene Therapy	Haemophilia B	Fidanacogene elaparvovec	Padua variant	Single intravenous infusion	Pfizer (Originally Spark)	Discontinued

		(formerly SPK-9001)	(rAAV-Spark100) (fidanacogene elaparvovec)			
Gene Therapy	Haemophilia B	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	Single intravenous infusion	CSL Behring (formerly uniQure)	Licensed
Gene Therapy	Haemophilia B	AMT-060 CSL220	Gene therapy using AAV5 vector encoding FIX	Single intravenous infusion	CSL Behring (Formerly uniQure)	Phase 1/2
Gene Therapy	Haemophilia B	AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	Single intravenous infusion	SJCRH	Phase 1
Gene Therapy	Haemophilia B	YUVA-GT-F901	Autologous HSC/MSC, modified with lentivirus encoding FIX	Single intravenous infusion	SGIMI	Phase 1
Gene Therapy	Haemophilia B	CB2679d-GT	Novel chimeric AAV vector Delivering an enhanced potency FIX	Single intravenous infusion	Catalyst Biosciences	Preclinical
Gene Therapy	Haemophilia B	BBM-H901	Engineered liver-tropic AAV vector expressing a hyperactive Padua FIX	Single intravenous infusion	Belief BioMed	Licensed in China in April 2025
Gene Therapy	Haemophilia B	-	CRISPR/Cas9-based Factor 9 (*F9*) gene-insertion therapy	Single intravenous infusion	Regeneron	Phase 2
Gene Therapy	von Willebrand Disease	-	CRISPR/Cas9 gene correction method using patient-derived endothelial colony forming cells	Single intravenous infusion	Dutch researchers with funding from Netherlands Organization for Scientific Research (NWO), Domain Applied and	Preclinical

					Engineering Sciences (TTW), 'Connecting Innovators' Open Technology Programme, Project#18712	

CELL BASED THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	Haemophilia A with inhibitors	TI-168	Autologous FVIII TCR-Treg cell therapy	-	TeraImmune Inc.	Phase 1/2a clinical trial planned for 2024, Orphan drug status granted by FDA
Cell-based therapy	Haemophilia B	BE-101	Engineered B Cell medicine	Single infusion	Be Biopharma	Discontinued

LICENSED FACTOR REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	VWD	Veyvondi® Vonvendi®	rVWF (vonicog alfa)	Takeda	Licensed
Replacement VWF, FVIII plasma-derived	VWD	Wilfactin	-	LFB	Licensed
Replacement VWF, FVIII plasma-derived	VWD	Fanhdi/ Alphanate	-	Grifols	Licensed
Replacement VWF, FVIII plasma-derived	VWD	Wilate	-	Octapharma	Licensed
Desmopressin	VWD	Octostim/ Emosint/ Minirin/Stimate	-	Ferring	Licensed
Replacement VWF plasma-derived	VWD, Haemophilia A	Voncento®	Human coagulation factor VIII and human von Willebrand factor	CSL Behring	Licensed
Replacement VWF plasma-derived	VWD, Haemophilia A	Haemate P®	Human coagulation FVIII and human von Willebrand factor	CSL Behring	Licensed
Replacement FVIII	Haemophilia A	Altuvoct® (formerly efanesoctocog alfa)	Ultra extended half-life FVIII (vWF fragments, XTEN Technology, and Fc Fusion)	Sobi/Sanofi	Licensed
Replacement FVIII	Haemophilia A	Advate®	Human coagulation factor VIII (rDNA), octocog alfa	Takeda	Licensed

Replacement FVIII	Haemophilia A	Adynovi® Adynovate® BAX855 TAK-660 SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	Licensed
Replacement FVIII	Haemophilia A	Afstyla® CSL627	rVIII-Single Chain	CSL Behring	Licensed
Replacement FVIII	Haemophilia A	Elocta® Eloctate®	rFVIIIFc (efmoroctocog alfa)	Sobi	Licensed
Replacement FVIII	Haemophilia A	Esperoct® N8-GP	rFVIII glycoPEGylated (turoctocog alfa pegol)	Novo Nordisk	Licensed
Replacement FVIII	Haemophilia A	Jivi® BAY 94-9027	rFVIII (damoctocog alfa pegol)	Bayer	Licensed
Replacement FVIII	Haemophilia A	Kogenate® FS	Recombinant FVIII	Bayer	Licensed
Replacement FVIII	Haemophilia A	Kovaltry® BAY 81-8937	Unmodified full-length rFVIII (octocog alfa)	Bayer	Licensed
Replacement FVIII	Haemophilia A	Novoeight®	rFVIII (turoctocog alfa)	Novo Nordisk	Licensed
Replacement FVIII	Haemophilia A	Nuwiq®	Human-cell-line-recombinant-human FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	Licensed
Replacement FVIII	Haemophilia A	Refacto AF®	moroctocog alfa	Pfizer	Licensed
Replacement FVIII	Haemophilia A	Octanate	-	Octapharma	Licensed

plasma-derived					
Replacement FVIII plasma-derived	Haemophilia A	Emoclot/Klott/ Emowil	-	Kedrion	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Beriate	-	CSL Behring	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Immunate	-	Takeda	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Factane	-	LFB	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Haemoctin	-	Biotest	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Koate DVI	-	Grifols	Licensed
Replacement FIX	Haemophilia B	Alprolix®	rFIXFc (eftrenonacog alfa)	Sobi	Licensed
Replacement FIX	Haemophilia B	BeneFIX®	nonacog alfa	Pfizer	Licensed
Replacement FIX	Haemophilia B	Idelvion®	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	Licensed
Replacement FIX	Haemophilia B	Refixia® / Rebinyn® rFIX-GP / N9-GP	Recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	Licensed
Replacement FIX	Haemophilia B	RIXubis®	nonacog gamma	Takeda	Licensed
Replacement FIX plasma-derived	Haemophilia B	Immunine/ Immunine Stim Plus	-	Takeda	Licensed
Replacement FIX plasma-derived	Haemophilia B	Octanine	-	Octapharma	Licensed

Replacement FIX plasma-derived	Haemophilia B	BETAFACT	-	LFB	Licensed
Replacement FIX plasma-derived	Haemophilia B	AimaFIX/IXED	-	Kedrion	Licensed
Replacement FIX plasma-derived	Haemophilia B	Alphanine	-	Grifols	Licensed
Replacement FXIII	Factor XIII deficiency	NovoThirteen®/ Tretten	Recombinant FXIII (catridecacog)	Novo Nordisk	Licensed
Plasma-derived fibrinogen concentrates	Fibrinogen disorders	CLOTTAFACT	-	LFB	Licensed
Plasma-derived fibrinogen concentrates	Fibrinogen disorders	RiaSTAP	-	CSL Behring	Licensed
Plasma-derived fibrinogen concentrates	Fibrinogen disorders	Fibryga	-	Octapharma	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Uman complex, Confidex, Beriplex, octaplex and cofact are prothrombin complex concentrates but they are not the only ones: there are also Proplex, Kedcom, Protromplex	-	Kedrion	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Confidex	-	CSL Behring	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Beriplex	-	CSL Behring	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Octaplex	-	Octapharma	Licensed

Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Cofact	-	Prothya Biosolutions	Licensed

LICENSED BYPASSING AGENTS					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	Haemophilia A or B w/ inhibitors	Sevenfact®/ Cevenfacta®	Recombinant FVIIa- jncw (eptacog beta)	LFB	Licensed in the US and Mexico (under brand name Sevenfact®) Licensed in Europe and the UK under brand name Cevenfacta®
Bypassing agent	Haemophilia A or B w/ inhibitors	NovoSeven® / NovoSeven® RT	Recombinant FVIIa (eptacog alfa)	Novo Nordisk	Licensed
Bypassing agent	Haemophilia A or B w/ inhibitors	Feiba	Activated prothrombin complex concentrate	Takeda	Licensed

LICENSED NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bi-specific monoclonal antibody	Severe and moderate Haemophilia A	Hemlibra®	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Roche	Licensed
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Concizumab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Novo Nordisk	Licensed
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Marstacimab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Pfizer	Licensed

LICENSED GENE THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Gene Therapy	Haemophilia A	Roctavian™ Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	Discontinued in May 2026
Gene Therapy	Haemophilia B	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	CSL Behring	Licensed
Gene Therapy	Haemophilia B	BEQVEZ® PF-06838435 fidanacogene elaparvovec (formerly SPK-9001)	Padua variant (rAAV-Spark100) (fidanacogene elaparvovec)	Pfizer	Discontinued

EHC

Empowering the bleeding disorders community