EHC
Empowering the bleeding disorders community

Novel Treatment Review (NTR)

A periodic EHC Review

January 2026 - Issue

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Foreword

Welcome to the first 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 American Society of Hematology (ASH) Annual Meeting held in December 2025, 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 August 1, 2025.

The second section, Report Highlights, summarises very concisely some of the key advances since the last edition of this review in August 2025 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:

ASH abstracts:
*https://submit.hematology.org/program?_gl=1*1hwmtv1*_ga*Mjc2NjUwMjU1LjE3NjUyNjg1NjE.*_ga_8L7E6EDKVZ*czE3NjU1NDk3NDkkbzYkZzEkdDE3NjU1NDk3OTIkajE3JGwwJGgw*_gcl_au*MTU4MzE0MzA2Ni4xNzY1MjY4NTUy*

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
- Prof Jan Blatny, EHC volunteer
- Prof Ana Boban, EHC volunteer
- Dr Radoslaw Kaczmarek, EHC volunteer
- Dr Ilmar Kruis, EHC volunteer
- Dr Maria Elisa Mancuso, EHC volunteer
- Asst Prof Brian O'Mahony, EHC volunteer
- Dr Uwe Schlenkrich, EHC volunteer
- Miguel Crato, EHC President
- Gaëtan Duport, EHC volunteer
- Prof Pratima Chowdary, EHC volunteer
- 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,

Miguel Crato, 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	*Subacromial decompression*
CVAD	*Central venous access device*	SC	*Subcutaneous*
CWA	*Clot waveform activity*	SD	*Standard deviation*
DNA	*Deoxyribonucleic acid*	TFPI	*Tissue factor pathway inhibitor*
DMC	*Data Monitoring Committee*	VWD	*Von Willebrand disease*

Summary

The January 2026 Novel Treatment Review (NTR) from the European Haemophilia Consortium (EHC) provides a comprehensive update on the evolving therapeutic landscape in haemophilia A, haemophilia B, von Willebrand disease (VWD), and related bleeding disorders. The edition focuses primarily on advances presented at the American Society of Hematology (ASH) Annual Meeting 2025, together with recent regulatory updates, clinical trial results, and pipeline developments. The objective of the NTR is to inform national member organisations and stakeholders about emerging innovations, safety considerations, and strategic trends reshaping care.

Evolving Treatment Landscape
The report highlights the continued shift away from traditional factor replacement toward non-replacement therapies (NRTs), FVIII mimetics, rebalancing agents, and gene therapies. These approaches aim to provide more durable bleed protection, improved convenience, and reduced treatment burden.

At the same time, ultra-extended half-life (UEHL) factor products are redefining replacement therapy by enabling higher sustained factor levels with less frequent dosing, improving protection and quality of life for many people with haemophilia. Alongside these, extended half-life factor products remain relevant for perioperative care and specific patient populations.

The document also includes updated tables of licensed products and therapies in development, helping contextualise innovation across modalities including bispecific antibodies, anti-TFPI agents, siRNA therapies, aptamers, and viral vector gene therapies.

FVIII Mimetics and Bispecific Antibodies
A major focus is on next-generation FVIII mimetics, particularly **NXT007** and **Mim8**. NXT007, an emicizumab-based bispecific antibody, demonstrates higher FVIII-mimetic activity and longer half-life than emicizumab. Phase I/II data show dose-dependent increases in thrombin generation and FVIII-like activity into the non-haemophilic range. Activated partial thromboplastin time (aPTT) shortens rapidly at low concentrations and plateaus at higher exposures, reflecting its FVIII-independent activation mechanism.

Clinical results show low annualised bleeding rates (ABRs) during maintenance dosing, with most patients experiencing zero treated bleeds. Safety findings are encouraging, with mainly mild injection-site reactions and no thrombotic events reported. Anti-drug antibodies were detected but had no meaningful impact on pharmacokinetics, safety, or efficacy. These data support progression to Phase III development.

Importantly, the report also addresses laboratory assay interference with NXT007. As with emicizumab, NXT007 strongly affects aPTT-based assays and can interfere with some PT-based tests at supratherapeutic concentrations. This has implications for routine monitoring and highlights the need for appropriate assay selection when managing patients receiving bispecific antibodies.

Mim8 data from the Phase 3 FRONTIER2 study show that once-weekly or once-monthly prophylaxis produces marked reductions in bleeding, with a high proportion of participants experiencing zero treated bleeds and no unexpected safety signals.

Rebalancing Therapies (Anti-TFPI and Others)

Rebalancing therapies continue to expand, particularly agents targeting the tissue factor pathway inhibitor (TFPI).

Marstacimab, recently approved for prophylaxis in haemophilia A and B without inhibitors, shows sustained reductions in bleeding and meaningful improvements in target joint outcomes. In the BASIS and open-label extension studies, most participants with pre-existing target joints experienced resolution over time, with progressively lower ABRs across both haemophilia A and B. Adolescents showed similar pharmacodynamic effects to adults, with pharmacokinetic differences largely explained by body weight. Safety remained favourable, with injection-site reactions as the most common adverse events and no thromboembolic signals observed.

Concizumab (Alhemo) is also discussed, including the implementation of personalised dose adjustment based on plasma concentrations following earlier safety concerns. Revised dosing strategies aim to optimise exposure while minimising thrombotic risk, demonstrating the importance of exposure-guided management in rebalancing therapy.

The report also explores interactions between rebalancing therapy and bypassing agents, such as the in-vitro evaluation of **eptacog beta** for managing breakthrough bleeds in patients receiving fitusiran prophylaxis. These studies support its potential clinical utility, while highlighting the need for careful assessment of thrombin generation and prothrombotic risk.

Gene Therapy Advances

Gene therapy remains a transformational area in haemophilia care. For haemophilia B, long-term results from the **HOPE-B trial of etranacogene dezaparvovec (Hemgenix)** confirm durable FIX Padua expression over five years, with sustained reductions in bleeding and minimal need for exogenous factor. Safety data show no late-onset hepatotoxicity or oncogenicity, reinforcing its benefit-risk profile.

Additional data from China using **AAV-FIX Padua vectors** show similar success, with mean FIX levels around 40 IU/dL at one year and ABRs reduced to near zero in many participants.

In haemophilia A, preclinical development continues with enhanced constructs such as **FVIII-QQ**, which demonstrate markedly increased hemostatic potency in animal models. These approaches aim to optimise FVIII activity while managing potential prothrombotic risks, which are under ongoing evaluation.

The report also highlights alternative approaches such as **AAV-based expression of FVIII-mimetic antibodies (Bi8)**, offering potential flexibility compared with classic FVIII transgene delivery.

Von Willebrand Disease Developments

The document includes early clinical experience with **VGA039**, a novel agent for VWD. Multiple-dose subcutaneous administration demonstrated good tolerability and substantial reductions in bleeding

compared with historical prophylaxis, with stable D-dimer levels and minimal safety concerns. These results support progression to Phase III development for once-monthly prophylaxis in VWD patients.`

Factor Replacement and Surgical Management

Despite innovation in NRTs and gene therapy, factor replacement remains essential, particularly in surgery. Data on extended half-life recombinant FVIII and FIX Fc fusion proteins show effective haemostatic control in major orthopaedic surgery with acceptable safety and manageable factor consumption, reinforcing the ongoing role of replacement therapy in complex clinical settings.

Section 1 - Recent marketing authorisations, indication expansion and early clinical trials

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

Novo Nordisk has submitted an application to the U.S. Food and Drug Administration and the European Medicines Agency (EMA) for approval to market Mim8 (denecimig), an injectable therapy designed to prevent bleeding episodes in individuals with haemophilia A, with or without inhibitors.

NHS England has expanded access to Roche and Chugai's emicizumab to all patients with moderate haemophilia A.

Rebalancing therapies

The U.S. Food and Drug Administration (FDA) has expanded the approval of Alhemo (concizumab), a once-daily subcutaneous therapy used to prevent or reduce bleeding episodes, to include people aged 12 years and older with haemophilia A or B without inhibitors.

Gene therapy for haemophilia A

BioMarin Pharmaceutical announce it is seeking to divest the rights to Roctavian (valoctocogene roxaparvovec), its approved gene therapy for haemophilia A.

Data from non-human primate studies indicate that the gene-editing therapy MGX-001 may restore clinically meaningful levels of factor VIII (FVIII) following a single dose, supporting its potential as a one-time treatment for haemophilia A.

In a presentation at ASH 2025, investigators reported that SPK-8011QQ, an investigational AAV gene therapy for haemophilia A designed to express a modified Factor VIII (FVIII-QQ) with enhanced resistance to activated protein C, demonstrated improved haemostatic potency in preclinical models. In mouse studies, SPK-8011QQ reduced bleeding and increased functional FVIII activity compared with controls, supporting continued evaluation of its efficacy and safety.

In a presentation at ASH 2025, I. Krivega et al. reported that non-viral ultrasound-mediated delivery of an episomal FVIII expression vector was safe and produced durable therapeutic levels of Factor VIII protein in non-human primate liver models. Ultrasound-mediated gene delivery (UMGD) enabled robust hepatic transfection with up to ~40 % of normal circulating FVIII levels detected, demonstrating efficient and redosable delivery of the FVIII transgene without unexpected safety signals, and no dose-limiting toxicities (DLTs) were reported in this preclinical study.

Gene therapy for haemophilia B

For the first time in a U.S. clinical trial, the cell therapy BE-101 has been administered to a patient with haemophilia B. Be Biopharma, the developer of BE-101, announced the dosing of the first participant in the first-in-human Phase 1/2 clinical trial, BeCoMe-9 (NCT06611436). The trial is designed to evaluate the safety and preliminary efficacy of a single dose of BE-101 in up to 24 adults with moderately severe to severe haemophilia B.

Other bleeding disorders

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency have expanded the approved indications for Vonvendi (recombinant von Willebrand factor) to include routine prophylactic use in adults with all types of von Willebrand disease, as well as on-demand treatment, management of bleeding episodes, and perioperative use in pediatric patients.

Hemab Therapeutics has secured $157 million in funding to advance the development of treatments for blood disorders, including Glanzmann thrombasthenia and von Willebrand disease. The company stated that the financing will support clinical trials of sutacimig (HMB-001), which is scheduled to enter a trial next year, as well as HMB-002, which has demonstrated proof of efficacy in early-stage studies.

Section 2 - Report highlights

An update on novel therapies in haemophilia A

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

NXT007

NXT007 prophylaxis in people with haemophilia A with or without FVIII inhibitors: A global Phase I/II multiple-ascending-dose study (Abstract 302, ASH 2025)

M. E. Mancuso et al. reported that NXT007 was well tolerated, with a tolerable safety profile in all dose cohorts. Treated bleed ABRs were low; one pt per cohort experienced a treated bleed in the maintenance period, except for one notable outlier in cohort 3 with multiple bleeds. The presence of ADA had no impact on PK. These data support progression to Phase III trials.

Bi8

Alternative AAV gene therapy for haemophilia A using expression of Bi8, a novel single-chain FVIII-mimetic antibody

At ASH 2025, the development of a liver-directed AAV8 gene therapy that encodes a compact single-chain FVIII-mimetic antibody (Bi8) to address limitations of current haemophilia A gene therapies was presented. In preclinical studies, AAV8-Bi8 produced durable, dose-dependent expression, fully corrected bleeding in FVIII-deficient mice at levels comparable to current treatments, and showed no toxicity or anti-drug immune responses, suggesting promise as a flexible and effective therapeutic platform.

Mim8

Mim8 prophylaxis in adults and adolescents with haemophilia A: 52-week efficacy and safety outcomes from the phase 3 FRONTIER2 study

In a presentation at ASH 2025, S. Lentz et al. reported that Mim8 prophylaxis was safe and well-tolerated in adults and adolescents with haemophilia A in the phase 3 FRONTIER2 study. Once-weekly and once-monthly subcutaneous prophylaxis with Mim8 resulted in marked reductions in annualised bleeding rates (ABR), with a high proportion of participants experiencing zero treated bleeds compared with on-demand or prior prophylaxis regimens, and no unexpected safety signals or dose-limiting toxicities (DLTs) were observed.

Factor Replacement Therapies

Efanesoctocog alfa (brand name **Altuvoct**)

Clinical outcomes up to 4 years of once-weekly efanesoctocog alfa prophylaxis in previously treated adults, adolescents, and children with severe hemophilia A: Interim analysis of the Phase 3 XTEND-ed long-term extension study (Abstract 539, ASH 2025)

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

An update on novel therapies in haemophilia B

Gene Therapy

Etranacogene dezaparvovec

End-of-study analysis of the HOPE-B trial confirms the durable efficacy and safety of etranacogene dezaparvovec hemophilia B gene therapy over 5 years (Abstract 538, ASH 2025)

S. Pipe reported the completed 5-year HOPE-B trial conclusively demonstrated that a single dose of etranacogene dezaparvovec delivers sustained, robust, endogenous FIX Padua expression, significantly reducing bleeding rates and the need for exogenous hemostatic support in most participants with severe or moderately severe hemophilia B. This gene therapy showed a favorable safety profile, with no late-onset AAV-related oncogenicity or hepatotoxicity observed. The positive benefit/risk ratio reported here highlights etranacogene dezaparvovec as a transformative therapy for individuals with hemophilia B. Consenting HOPE-B participants will be monitored long-term until 15 years post-treatment in the IX-TEND 3003 study.

An Update on Rebalancing Therapies

Concizumab

Concizumab plasma concentration measurements for personalized dose adjustment in patients with Hemophilia A/B with and without inhibitors: Data from the Phase 3 explorer7 and explorer8 studies (Abstract 3070, ASH 2025)

H. Eichler et al. presented that the findings support the use of concizumab plasma concentration-guided dose adjustments to optimize prophylaxis in patients with hemophilia A or B, with or without inhibitors. Exposure-response analyses confirmed the validity of the selected lower (200 ng/mL) and upper (4,000 ng/mL) limits of concizumab plasma concentration and showed that dose adjustments can effectively personalize therapy to reduce bleeding rates.

An update on novel therapies in von Willebrand disease and other rare bleeding disorders

VGA039

Subcutaneous, every-four-week maintenance dosing of a novel protein S antibody is well-tolerated and substantially reduces bleeding rates: Results from A phase 1/2 multidose study of VGA039 in patients with von Willebrand disease

In a presentation at ASH 2025, A. Wheeler et al. reported that subcutaneous every-four-week maintenance dosing of a novel protein S antibody was well-tolerated and substantially reduced bleeding rates in the phase 1/2 multidose study in patients with bleeding disorders. Maintenance dosing led to marked reductions in annualised bleeding rates (ABRs) with associated pharmacodynamic effects suggesting improved hemostasis at therapeutic exposures, and no unexpected safety signals or dose-limiting toxicities (DLTs) were observed across dose cohorts.

Section 3 - research abstracts and articles

Haemophilia A

Bispecific Monoclonal Antibodies Mimetics (including FVIII Mimetics)

Emicizumab (Hemlibra)

AOZORA study: 3-year interim analysis of safety and joint health in pediatric people with hemophilia A receiving emicizumab prophylaxis (RPTH 2025)

M. Shima et al

Background: Recurrent joint bleeding in people with hemophilia A (PwHA) can cause hemophilic arthropathy, resulting in limited movement and chronic pain. Emicizumab is a bispecific monoclonal antibody bridging activated factor (F)IX and FX to substitute for deficient activated FVIII in PwHA, thereby improving hemostasis.

Objectives: This 3-year interim analysis of the ongoing, open-label, phase IV AOZORA study (jRCT1080224629) analyzes medium-term safety and joint health in pediatric PwHA without FVIII inhibitors receiving emicizumab.

Methods: PwHA aged <12 years with severe hemophilia A without FVIII inhibitors were eligible. Participants entered AOZORA as emicizumab-naïve or having previously initiated emicizumab during the HOHOEMI study. Endpoints included safety, and joint health, as assessed by magnetic resonance imaging and Hemophilia Joint Health Score (HJHS). Participants will receive emicizumab for 6 years.

Results: A total of 30 male PwHA were enrolled. Data cutoff was the last day of week 145 for each participant. Median (range) age was 4.2 (0.7-11.1) years, and 27 of the 30 (90.0%) had received prior FVIII prophylaxis. The emicizumab safety profile was confirmed. No thrombotic events/microangiopathies occurred. All joints with synovial hypertrophy and hemosiderin resolved or improved by week 145. HJHS remained at 0 from week 1 to week 145 for 18 (66.7%) participants; overall, there was no worsening trend in HJHS over time. Model-based annualized bleeding rate (95% CI) for treated bleeds was 3.6 (2.04-6.46) prior to emicizumab and 0.8 (0.47-1.22) after receiving emicizumab.

Discussion/Conclusion: Emicizumab is well tolerated and appears to maintain or improve joint health in pediatric PwHA.

Health-Related Quality of Life, Physical Activity and Joint Health in People With Severe Haemophilia A Receiving Emicizumab: Results From the Phase IV HemiNorth 2 Study (Haemophilia 2025)

J. Astermark et al

Introduction: Despite factor (F)VIII prophylaxis, a perceived increased risk of bleeding for some people with severe haemophilia A (PwSHA) exists, limiting physical activity (PA) and restricting quality of life (QoL).

Aim: HemiNorth 2 (EudraCT# 2020-003256-32) is an interventional study evaluating the impact of switching from FVIII prophylaxis to emicizumab in PwSHA without FVIII inhibitors who have a need for improved prophylaxis in the Nordic countries.

Methods: Following completion of the HemiNorth non-interventional study (NIS), eligible participants (aged ≥ 12–61 years) were enrolled in HemiNorth 2. The primary endpoint was health-related QoL via the Comprehensive Assessment Tool for Challenges in Hemophilia (CATCH). Secondary endpoints included PA (International Physical Activity Questionnaire-Short Form [IPAQ-SF]), treatment preference (Emicizumab Preference [EmiPref] survey), joint health, model-based annualised bleeding rates (ABRs) and adverse events.

Results: Overall, 28 physically active male PwSHA were enrolled. Most baseline CATCH domains were ≤ 25 and remained consistent; mean treatment burden considerably improved from baseline for adults (−17.8) and adolescents (+16.7). IPAQ-SF scores were consistent throughout the study. Overall, 23 of 25 (92.0%) EmiPref respondents preferred emicizumab over FVIII prophylaxis. Model-based ABRs for treated bleeds decreased from 5.9 (95% confidence interval [CI]: 3.8–9.1) to 1.6 (95% CI: 0.9–3.0) from the NIS to HemiNorth 2, and participants with zero treated bleeds increased from 8 (28.6%) to 16 (57.1%). No new safety signals were reported.

Conclusions: Emicizumab improved treatment burden and was preferred by most participants over FVIII prophylaxis. PA levels were consistently high, and bleeding rates improved with emicizumab versus prior FVIII prophylaxis.

Emicizumab in Previously Untreated Patients and Minimally Treated Patients With Hemophilia A: A Comparative Study Between Two International Cohorts (Pediatric Blood & Cancer 2025)

S. Levy-Mendelovich et al

Background: Hemophilia A (HA) is a rare bleeding disorder caused by coagulation factor VIII (FVIII) deficiency. Prophylactic FVIII replacement therapy is essential for preventing bleeds, but it carries a risk of inhibitor development, especially in previously untreated and minimally treated patients (PUPs and MTPs, respectively). Emicizumab, a bispecific monoclonal antibody that mimics FVIII function, offers a promising alternative for HA prophylaxis due to its subcutaneous administration and favorable safety profile.

Methods: This study evaluated the real-world safety and efficacy of emicizumab prophylaxis in two international hemophilia treatment centers (HTC). The first HTC included a cohort of 22 MTPs with severe HA (FVIII <1%) and fewer than five prior FVIII exposure days, while the second HTC enrolled 19 PUPs with severe HA.

Results: The median age at emicizumab prophylaxis initiation was 5 months for the MTPs and 8 months for the PUPs. Patients were followed for a median of 27 and 29 months, respectively. The median time to first bleed was 13 months for MTPs, with a significantly longer time to first bleed noted in the PUPs cohort. Safety outcomes were favorable, with neither intracranial hemorrhage nor

anti-emicizumab antibodies reported. Four patients, 18% of all MTPs, developed FVIII inhibitors, all associated with high-risk genetic mutations and prior bleeding events.

Conclusions: Our findings support the early use of emicizumab as a safe and effective prophylactic strategy in infants with severe HA. However, the observed inhibitor rate underscores the need for ongoing monitoring and research to optimize care, particularly in vulnerable populations.

Evolution of joint health and physical activity in people with hemophilia A without factor VIII inhibitors switching to emicizumab prophylaxis: A second interim analysis of the BEYOND ABR study (Abstract 1285, ASH 2025)

R. Kruse-Jarres et al

Background: Advances in hemophilia A (HA) treatment have led to lower bleeding rates (Srivastava et al. Haemophilia 2020), shifting focus toward functional endpoints such as joint health. Despite treatment with factor (F)VIII prophylaxis, joint health has been observed to deteriorate over time (Arvanitakis et al. Haemophilia 2024). BEYOND ABR (NCT05181618) aims to evaluate joint health and physical activity outcomes in people with HA (PwHA) switching from FVIII prophylaxis to emicizumab. This second interim analysis reports data analyzed after 12 months of treatment with emicizumab.

Methods: BEYOND ABR is a Phase IV, multicenter, open-label study in PwHA aged 13-69 years with moderate/severe HA without FVIII inhibitors. Joint health for ankles, knees, and elbows is evaluated in participants' joints without pre-study surgery/procedures using the Hemophilia Joint Health Score (HJHS) 2.1. Numerical changes in problem joint counts (defined as per Chowdary et al. Haemophilia 2023) from baseline are captured by both participants and investigators. Target joint resolution is assessed in participants with ≥52 weeks of follow-up. Physical activity is measured using the International Physical Activity Questionnaire (IPAQ). The number of participants with zero treated bleeds is determined using data from a Bleeds and Medication Questionnaire. The Emicizumab Preference Survey was carried out following 6 months of emicizumab treatment.

Results: Overall, 136 PwHA were enrolled, all male with varying levels of joint status/impairment. At the single joint level, mean (standard deviation [SD]) HJHS total score was 2.3 (3.5) at baseline and improved by -0.3 (1.7) at Month 6 and -0.5 (1.9) at Month 12. At Month 6, 93/726 (12.8%) joints showed an improvement of ≥2 points, increasing to 119/696 (17.1%) at Month 12; 41/726 (5.6%) joints and 42/696 (6.0%) joints showed a worsening of ≥2 points at Month 6 and Month 12, respectively.

At the participant level, the mean (SD) HJHS sum of joints (excluding Global Gait Score; maximum score: 120, calculated as 6 joints × 10 points each) was 10.1 (13.2) at baseline and improved by -2.0 (6.4) at Month 6 and -2.8 (7.9) at Month 12. In total, 23/88 (26.1%) participants reported an improvement of ≥4 points in HJHS sum of joints from baseline to Month 12 and 5/88 (5.7%) reported worsening of ≥4 points at Month 12.

At Month 12, the number of participant-reported problem joints had decreased from baseline in 35/117 (29.9%) participants, including resolution of ≥2 problem joints in 16 (13.7%) participants. Conversely, 16/117 (13.7%) participants reported an increase in the number of problem joints from baseline, including an increase of ≥2 problem joints in 8 participants (6.8%). The number of investigator-reported problem joints reduced in 33/131 (25.2%) participants at Month 12; 13 (9.9%)

participants had ≥2 resolved problem joints. Overall, 19/131 (14.5%) participants had an increase in investigator-reported problem joints, including 14 (10.7%) with an increase of ≥2 problem joints. In participants who remained in the study for at least one year, 27/27 (100%) baseline target joints in 15 participants had resolved at Month 12.

In participants with valid IPAQ data at baseline and/or 3 months and/or 12 months after switching to emicizumab, the proportion of participants in the low physical activity category decreased from 30.8% (32/104) at baseline to 22.3% (23/103) at Month 3, and remained stable at Month 12 (23.4% [22/94]). The proportion of participants in the high physical activity category increased from 44.2% (46/104) to 52.4% (54/103) at Month 3, and was 50.0% (47/94) at Month 12.

Zero treated bleeds were reported by 110/136 (80.9%) participants between Weeks 1 and 24, and 105/134 (78.4%) between Weeks 25 and 48.

At Month 6, 125/130 (96.2%) participants preferred emicizumab to their previous FVIII prophylaxis, while only 1/130 (0.8%) preferred their previous treatment; 4/130 (3.1%) had no preference.

Conclusions: In the first 12 months after switching from FVIII prophylaxis to emicizumab, participants had low bleeding rates associated with numerical improvements in joint health, as measured with HJHS, plus a reduction in the number of problem and target joints. Overall, physical activity levels assessed with IPAQ were stable or showed a shift towards higher activity levels, and most participants preferred emicizumab compared with their previous treatment. Follow-up will continue for 3 years.

Exploratory analysis from HAVEN 1–4 to further contextualize injection-site reactions among people with hemophilia A receiving emicizumab (Abstract 4839, ASH 2025)

M. Bloomberg et al

Background: Long-term data with subcutaneous emicizumab prophylaxis in people with hemophilia A (PwHA) with or without factor (F)VIII inhibitors indicated low bleed rates and that emicizumab was well tolerated across the Phase III HAVEN 1-4 clinical studies (NCT02622321/NCT02795767/NCT02847637/NCT03020160; Callaghan et al. Blood 2021). Over a median emicizumab duration of 130.3 weeks (range: 3.4-221.1), the most common treatment-related adverse events were injection-site reactions (ISRs). Almost all were mild and occurred during the first 24 weeks, with the proportion of participants with ISRs declining over time to <1% of the safety population. This exploratory analysis further contextualizes ISRs across HAVEN 1-4, informing on the tolerability of emicizumab injections.

Methods: This analysis includes PwHA who received emicizumab in the HAVEN 1-4 clinical studies. The study populations in the four Phase III studies included PwHA ≥12 years old with FVIII inhibitors (HAVEN 1 and 4), PwHA ≥12 years old without FVIII inhibitors (HAVEN 3 and 4), and PwHA <12 years old with FVIII inhibitors (HAVEN 2). Maintenance doses of emicizumab in the studies included 1.5mg/kg once weekly (HAVEN 1, 2, and 3), 3.0mg/kg every 2 weeks (HAVEN 2 and 3), or 6.0mg/kg every 4 weeks (HAVEN 2 and 4). The schedule of clinic visits during the HAVEN 1-4 studies was identical across the studies until Week 49 (HAVEN 2) or Week 73 (HAVEN 1, 3 and 4); following this, the schedule of follow-up visits was similar across the studies, with clinic visits every 12 weeks (HAVEN 1, 2 and 4) or every 24 weeks (HAVEN 3). Exploratory outcomes were assessed in the total

safety population, and included the proportion of participants with ISRs over 24-week intervals, and the proportion of total emicizumab injections associated with an ISR (total ISRs divided by [mean number of doses per participant multiplied by the number of treated participants]). ISR events considered here are those reported as localized ISR with associated symptoms.

Results: The safety population totaled 399 PwHA, including 132 participants (33.1%) aged <18 years old.

The median emicizumab duration was 130.3 weeks (range: 3.4-221.1), and 389 participants (97.5%) had a duration >52 weeks. A total of 112 participants (28.1%) had ≥1 ISR. In the overall population, the median number of ISRs per participant was 0 (range: 0-23). The proportion of participants with ISRs declined over time from 23.3% in the first 24 weeks, 4.8% at 25-48 weeks, 2.5% at 49-72 weeks, 1.3% at 73-96 weeks, and <1% thereafter.

In total, 317 ISRs occurred out of over 42,000 injections, reflecting that 0.75% of injections were associated with a reported ISR. When split by study, the percentage of ISRs by total injections was 0.42% in HAVEN 1, 0.98% in HAVEN 2, 0.65% in HAVEN 3, and 3.29% in HAVEN 4. No participant discontinued emicizumab because of an ISR.

The top three most common recorded symptoms associated with ISRs were: erythema, occurring in 52 participants (46.4% of the total 112 participants with an ISR); pain, occurring in 18 participants (16.1%); and swelling, which occurred in 16 participants (14.3%). Type and incidence of symptoms associated with ISR were similar irrespective of emicizumab dosing regimen. Symptoms associated with ISRs trended down over time intervals across all four clinical studies and across all emicizumab dosing regimens.

Conclusions: These data in PwHA receiving emicizumab prophylaxis across the four Phase III HAVEN 1-4 clinical studies show that the proportion of participants that experienced ISRs declined over time to <1%, with 0.75% of over 42,000 injections being associated with an ISR. However, it is important to acknowledge that changes in visit schedules beyond the main phase of the studies may introduce a reporting bias. The results from this analysis expand our understanding of the tolerability of emicizumab injections in PwHA.

AKATSUKI third interim analysis: Safety of emicizumab during and after immune tolerance induction implementation (Abstract 303, ASH 2025)

K. Nogamil et al

Background: Immune tolerance induction (ITI) therapy is recommended to eradicate factor (F)VIII| inhibitors in people with hemophilia A (PwHA). There are limited safety data available on emicizumab in combination with ITI, particularly concerning thrombotic events (TEs), with ITI efficacy also a subject of interest. This study presents the safety of emicizumab during and directly following ITI.

Methods: AKATSUKI (jRCTs041200037) is a Phase IV, prospective, open-label, multicenter study. Eligible PwHA had a positive FVIII inhibitor titer (≥0.6 BU/mL) and would begin ITI therapy after study enrollment, or were undergoing ITI therapy but had not met the criteria for partial ITI success. PwHA with FVIII inhibitors received an approved emicizumab dosing regimen and ITI therapy. ITI dosing regimens included 50 IU/kg standard half-life (SHL) or extended half-life (EHL) FVIII

concentrate administered three times a week; for EHL FVIII, a dosing frequency of twice per week was permitted. Further details, including post-ITI maintenance dosing regimens, have been published (Matsushita, BMJ Open 2022). The primary endpoint was evaluation of adverse events (AEs), including TEs, and abnormal clinical laboratory values during and immediately after ITI. Secondary endpoints included number of treated bleeds, number of participants who started ITI after study entry who achieved ITI partial success, and changes in FVIII inhibitor titer during ITI and after achieving partial success. Partial success was defined as a negative FVIII inhibitor test result combined with a normal FVIII recovery value in the participant's blood sample.

Results: Twelve male participants (median [range] age at entry: 2.5 [1-54] years) enrolled. Participants received emicizumab (n=11), ITI (n=9), or both (n=7) before enrollment; one participant received emicizumab and ITI separately, with no treatment overlap. The median (range) duration of ITI before enrollment was 536 (12-1,734) days. Three participants began ITI after enrollment, all aged <2 years. This interim analysis was performed 144 weeks after the first study dose of emicizumab in the last enrolled participant (evaluation period, median [range]: 1079.5 [224-1,342] days; data cut-off: October 31, 2024). Three participants used SHL FVIII and nine participants used EHL FVIII for ITI therapy. Overall, 90 AEs were reported and there were no TEs. One Grade 1 event of swelling was considered emicizumab-related, but this resolved the same day it occurred. Three participants experienced a serious AE (SAE), all of which resolved and were considered unrelated to emicizumab or FVIII concentrate. There was one abnormal laboratory value: a Grade 1 prolonged activated partial thromboplastin time influenced by heparin administration. In total, 22 treated bleeds were reported in seven participants: one spontaneous, two surgical and 19 traumatic. Of these, 16 were managed with recombinant activated FVII, six were managed with EHL FVIII and none treated with activated prothrombin complex concentrate. Median annualized bleeding rate during the study period was 0.44 (range: 0.00-2.09).

By data cut-off, six participants, all with a history of ITI before study entry, achieved negative FVIII| inhibitor status. Median (range) duration of ITI at study entry for these participants was 381 (12-1,734) days and median (range) duration of ITI during the study, up to the point at which a negative FVIII inhibitor status was achieved, was 93 (5-137) weeks. Of these six participants, three maintained continuous FVIII inhibitor negativity during the observation period. Three participants had achieved partial ITI success by data cut-off, though recurrence of FVIII inhibitors occurred in two participants. Of these, one participant experienced FVIII inhibitor recurrence 12 days after partial ITI success was achieved (FVIII inhibitor level = 0.97 BU/mL), the other experienced recurrence 16 days after partial ITI success was achieved (FVIII inhibitor level = 1.82 BU/mL).

Conclusions: At this 144-week interim analysis, no new safety concerns or TEs were reported. Effective bleed control was confirmed with a combination of emicizumab and ITI. Of the 12 participants enrolled, three achieved partial ITI success, though two participants had recurrence of FVIII inhibitors. Negative inhibitor status was reported in six participants. AKATSUKI continues to evaluate the safety of emicizumab during, and following, ITI therapy in PwHA with FVIII inhibitors.

Use of emicizumab in patients with acquired hemophilia A: An interim safety analysis of a large-scale post-marketing surveillance study (Abstract 4854, ASH 2025)

M. Shima et al

Background: Acquired hemophilia A (AHA) is a rare autoimmune disorder in which autoantibodies neutralize coagulation factor VIII (FVIII), causing bleeding. Treatment focuses on bleeding control using bypassing agents and elimination of FVIII inhibitors via immunosuppressive therapy (IST). Emicizumab is a recombinant humanized bispecific monoclonal antibody that mimics activated FVIII (FVIIIa) by bridging FIXa and FX to promote hemostasis. Its safety and efficacy in congenital HA have been established. Following the Phase 3 AGEHA trial (Shima, JTH 2023), emicizumab was approved in Japan in 2022 for AHA. While strict discontinuation criteria for emicizumab are not defined, the manufacturer suggests considering it when FVIII activity exceeds 50 IU/dL, as in AGEHA. This post-marketing surveillance study aimed to monitor the safety of emicizumab, and indirectly assess its effectiveness, for patients with AHA in real-world clinical practice.

Methods: This ongoing observational study (UMIN000048156) includes a longitudinal series of patients with AHA treated with emicizumab from August 2022 to July 2025. This planned interim analysis was conducted after 50 patients completed the observation period. Each patient was followed from first emicizumab dose until 4 weeks after last administration, with a maximum observation period of 24 months. Inclusion criteria were confirmed AHA diagnosis and emicizumab treatment at one of 37 medical institutions. The primary endpoint was adverse events (AEs); if a causal relationship with emicizumab could not be ruled out, the event was classed as an adverse drug reaction (ADR).

Results: At the time of this interim analysis, 110 patients were enrolled in the study; 51 completed observation and are included here. Of these, 34 (66.7%) were male; median age was 76.0 years (range: 33-91). All 51 patients received IST, most commonly prednisolone monotherapy (n=29; 56.9%). Median initial prednisolone dose for AHA treatment, either as monotherapy or IST combination, was 0.93 mg/kg (mean [SD]: 0.79 [0.32] mg/kg). Median FVIII activity before emicizumab was 1.0 IU/dL (range: 0.0-15.0); at treatment end, it was 59.1 IU/dL (15.1-103.0). Median FVIII inhibitor titer decreased from 34.1 BU/mL (1.3-401.4) to 0.9 BU/mL (0.0-48.8). AEs occurred in 25 (49.0%) patients, totaling 63 events (45 serious), with infection the most common (n=10; 19.6%). One thromboembolism (cerebral infarction) was deemed unrelated to emicizumab by the investigator. Two ADRs were reported by investigators, both classed as serious: acute pyelonephritis and hemorrhoidal hemorrhage.Nine (17.6%) patients died during the observation period; causes of death were infection (n=4; 7.8%), hemorrhage (n=3; 5.9%), interstitial lung disease (recurrent lung cancer; n=1), and cholangiocarcinoma with liver metastases (n=1). Hemorrhage-related deaths included: upper gastrointestinal bleeding (treated with 23 doses of rFVIIa and red blood cell [RBC] and platelet transfusions), bladder hemorrhage (treated with 8 doses of rEVIIa and RBC transfusion), and gastric ulcer bleeding (treated with 1 dose of rFVIIa and RBC transfusion). All three patients, who had multiple comorbidities, received prednisolone monotherapy, but FVIII activity had not recovered. A causal relationship with emicizumab was ruled out in all deaths. During emicizumab treatment, 21/51 (41.2%) patients used rFVIIa, 9/51 (17.6%) had transfusions, and 7/51 (13.7%) received other hemostatic agents (FXIII, tranexamic acid. No patient received activated prothrombin complex concentrate or FVIIa/FX. Hemostatic treatment declined over time. Among 38 patients who did not receive rFVIIa in the first week after emicizumab initiation, 30/38 (78.9%) required no rFVIIa throughout the study, indicating prevention of new treated bleeds in almost 80% of cases. Of 301 rFVIIa doses administered following initiation of emicizumab, 181 were given to 4 patients for treatment of bleeds: gastrointestinal (n=2), iliopsoas/retroperitoneal/catheter removal (n=1), and unknown location (n=1).

Conclusions: In this large-scale post-marketing study, emicizumab demonstrated a favorable safety profile in real-world clinical practice. While the study was not specifically designed to evaluate efficacy, the consistently low incidence of bleeding events observed supports the potential role of emicizumab in effectively preventing bleeds in patients with AHA, reinforcing its positive risk-benefit profile at this interim analysis.

NXT007

NXT007 prophylaxis in people with hemophilia A with or without FVIII inhibitors: A global Phase I/II multiple-ascending-dose study (Abstract 302, ASH 2025)

M. E. Mancuso et al

Background: NXT007 is a next-generation bispecific antibody, based on emicizumab, that mimics the cofactor function of activated factor (F)VIII to restore intrinsic tenase activity in people with hemophilia A (PwHA). In comparison with emicizumab, NXT007 has demonstrated greater potency and higher maximum effect in thrombin generation (TG) analysis, and has a longer half-life. NXT007 was first investigated in PwHA in the multiple-ascending-dose (MAD) part of the Phase I/II NXTAGE study (Shima et al. OC 20. ISTH 2025); after a median of 68.4 weeks of follow-up, there were no safety concerns at any dose and the two highest dose cohorts had zero treated bleeds. Here, we report on the first three cohorts of the Phase I/II global MAD study of NXT007 in PwHA.

Methods: The global MAD study of NXT007 (NCT05987449) is an open-label, non-randomized, multicenter trial. Eligible participants (pts) are males aged 12-59 years with a diagnosis of severe (FVIII activity <1 IU/dL) or moderate (FVIII activity 1-5 IU/dL) congenital HA with/without FVIII inhibitors.

The primary treatment phase was 24 weeks. Each cohort received two loading doses of subcutaneous NXT007 at Days 1 and 15, followed by maintenance doses every 4 weeks from Day 29. The loading doses for cohorts 1, 2, and 3, were 0.42mg/kg, 1.05mg/kg, and 1.62mg/kg, respectively. Maintenance doses were 0.28mg/kg, 0.70mg/kg, and 1.08mg/kg, respectively; these were the same doses given to NXTAGE cohorts B2-B4, to be comparable at steady state. Pts may continue their NXT007 maintenance dose for up to 7 years in the extension phase.

The primary objective is to investigate the safety of NXT007, including incidence of adverse events (AES) and serious AEs (SAEs). Secondary and exploratory objectives include efficacy (annualized bleeding rate [ABR] using the ISTH-SSC 72-hour rule and a negative binomial regression model), pharmacokinetics (PK), pharmacodynamics (including TG), D-dimer measurement, and immunogenicity (incidence of anti-drug antibodies [ADA]).

Results: At data cut-off (April 21, 2025), 22 pts had been treated with NXT007: seven in cohort 1, nine in cohort 2, and six in cohort 3. One pt left the study prior to any NXT007 administration due to meeting an exclusion criterion. No pt discontinued NXT007 treatment.

At enrollment, the median (range) age of pts was 36 (15-49) years. Twenty (90.9%) pts had severe HA and 2 (9.1%) had moderate HA. Nineteen (86.4%) pts had no history of FVIII inhibitors, 2 (9.1%)

had previous and 1 (4.5%) had current FVIII inhibitors. Median (range) observation period in cohorts 1, 2, and 3 was 68.9 (61.1-80.0), 44.1 (42.1-46.1), and 21.6 (20.1-24.1) weeks, respectively.

At data cut-off, 6/7 (85.7%) pts in cohort 1 had experienced a total of 47 AEs; 8/9 (88.9%) pts in cohort 2 had 26 AEs; and 5/6 (83.3%) pts in cohort 3 had 23 AEs. Of 285 NXT007 administrations, 29 (10.2%) in five pts were associated with an injection-site reaction, all of which were Grade 1 and resolved by data cut-off. One other pt, in cohort 2, experienced AEs considered to be related to NXTO07: transient Grade 2 aspartate aminotransferase increase and Grade 1 alanine aminotransferase increase. Two pts experienced SAEs, both of which resolved and were considered unrelated to NXTO07: a pt in cohort 2 had Grade 3 adjustment disorder and a pt in cohort 3 had a Grade 3 fall. There were no thrombotic events or thrombotic microangiopathies.

ABRs (95% confidence intervals) for treated bleeds in the maintenance period were 0.11 (0.02-0.81) for cohort 1, 0.15 (0.02-1.04) for cohort 2, and 1.94 (0.73-5.16) for cohort 3. During the maintenance period, 6/7 (85.7%) pts in cohort 1, 8/9 (88.9%) in cohort 2, and 5/6 (83.3%) in cohort 3 had zero treated bleeds.

NXT007 plasma concentrations increased dose dependently and in line with population PK simulations.

Activated FXI-triggered TG peak height increased from baseline and with increasing NXT007 plasma concentrations, into the non-hemophilic range. D-dimer levels were unaffected by NXT007. ADA were detected in most pts, but had no impact on PK, safety, or efficacy, and no cross-reactivity with emicizumab.

Conclusions: NXT007 was well tolerated, with a tolerable safety profile in all dose cohorts. Treated bleed ABRs were low; one pt per cohort experienced a treated bleed in the maintenance period, except for one notable outlier in cohort 3 with multiple bleeds. Presence of ADA had no impact on PK. These data support progression to Phase III trials.

Effects and interferences of NXT007, a novel bispecific antibody, on coagulation assays (Abstract 1275, ASH 2025)

A. Kiialainen et al

Background: NXT007 is a bispecific antibody that mimics the function of activated factor (F)VIII and is currently in clinical development for treatment of hemophilia A (HA). NXT007 was engineered and optimized based on emicizumab, which has been shown to interfere with some standard coagulation assays (Adamkewicz et al. Thromb Haemost 2019). The effects of NXT007 in various standard coagulation assays with clotting, chromogenic and immunologic reaction principles were evaluated.

Methods: NXT007 was spiked into healthy volunteer, HA, and FV Leiden thrombophilia plasmas at concentrations of 0, 10, 30 and 100 ug/mL. Plasma samples analyzed for activated partial thromboplastin time (aPTT), and those for the anti-Xa assay, were also spiked with unfractionated heparin to final concentrations of 0.5 and 1.0 IU/mL. Samples with known high international normalized ratio (INR) and D-dimer levels were also used for prothrombin time (PT) and D-dimer assays, respectively. aPTT (Siemens), thrombin time (TT; Stago), PT (Stago, Siemens, and Instrument Laboratories [IL]), derived fibrinogen (IL), Clauss fibrinogen (Stago), activated protein C resistance (APC-R) FV Leiden (Pentapharm), anti-Xa (Stago), antithrombin activity (Stago), plasminogen

activity (Stago), plasminogen antigen (Abcam), protein C chromogenic (Stago), protein C aPTT-based (Stago), protein S aPTT-based (Stago), protein S PT-based (IL), D-dimer (Stago), von Willebrand factor (VWF) antigen (IL), VWF activity (IL), FXIII antigen (IL), aPTT-based single factor (Siemens), PT-based single factor (Stago), and chromogenic FIX (Hyphen BioMed) assays were all performed according to the manufacturers' instructions.

Results: NXT007 had a strong effect on aPTT, which decreased to below the limit of detection (<20s) at 10 ug/mL of NXT007 and above in all plasmas. In the presence of heparin, aPTT was prolonged when no NXT007 was present and decreased with increasing NXT007 concentration. Increased INR values were seen at 100 ug/mL NXT007, which is a supratherapeutic level, with all three PT assays tested. Increasing INR values with increasing NXT007 concentrations were observed in samples that had elevated INRs (INR 2-3) before spiking with NXT007. NXT007 had a strong effect on aPTT-based single factor assays (FVIII, FIX, FXI and FXII). In contrast, NXT007 did not interfere with PT-based single factor assays (FII, FV, FVII and FX). NXT007 had no effect on TT. A decrease in PT-derived fibrinogen concentration was seen with increasing NXT007 concentration, but there was no effect on fibrinogen concentration measured by Clauss fibrinogen assay. NXT007 had no effect on APC ratios by PT-based APC-R FV Leiden assay, heparin potency measurements with the anti-Xa assay, anti-thrombin activity, plasminogen activity or antigen concentration. In the aPTT-based protein C and protein S assays, protein C and protein S concentrations decreased with increasing NXT007 concentration. NXT007 had no impact on chromogenic protein C or PT-based protein S concentrations. NXT007 had no impact on D-dimer measurement, VWF antigen or activity, or FXIII antigen concentration. Chromogenic FIX activity decreased at 100 ug/mL NXT007.

Conclusions: As expected based on its mode of action, and similar to emicizumab, NXT007 had a very strong effect on aPTT that resulted in interference with all aPTT-based assays. NXT007 also affected PT at the supratherapeutic concentration of 100 ug/mL, potentially due to inhibition of FX. PT was also affected in samples with an already increased INR. NXT007 interfered with the PT-based derived fibrinogen assay, but not with the PT-based single-factor assays or other PT-based assays (APC-R or protein S). It has been previously shown that NXT007 has different effects on chromogenic FVIII activity assays depending on the species of origin of the FIX and FX in those assays (Kilalainen et al. ISTH 2024: PB0252). In this study, NXT007 affected chromogenic FIX activity at high concentration (100 ug/mL). NXT007 had no effect on other chromogenic assays or on assays with immunologic reaction principles. Coagulation assay interference should be considered when selecting assays for measuring samples from people with HA receiving NXT007, and when interpreting the results of those measurements.

Pharmacodynamic biomarkers in people with hemophilia A receiving multiple ascending doses of NXT007 (Abstract 4841, ASH 2025)

A. Kiialainen et al

Background: NXT007 is a bispecific, monoclonal antibody that mimics the function of activated factor (F)VIII. NXT007 was engineered and optimized based on emicizumab. The Phase I/II multiple ascending dose (MAD) study of NXT007 (NCT05987449) is an open-label, non-randomized, multicenter trial, testing increasing subcutaneous doses of NXT007 in people with hemophilia A (PwHA). NXT007 demonstrated comparable thrombin generation (TG) to FVIII levels in the non-hemophilia range in in vitro spiking experiments (Teranishi-Ikawa et al. J Thromb Haemost 2024). Here, we present the pharmacodynamic (PD) and exploratory biomarker data, as well as pharmacokinetic-PD relationships, from this NXT007 study.

Methods: Prior to starting NXT007, participants received one dose of 40 IU/kg of their standard-of-care FVIII treatment during a pre-treatment visit. This dose, based on an average in vivo recovery

(IVR) of 2 IU/dL per IU/kg, was expected to achieve plasma FVIII activity of approximately 80 IU/dL. Plasma samples were collected prior to FVIII infusion and 15 minutes (min), 1 hour (h) and 3 h post infusion. During the NXT007 treatment period, samples were collected prior to loading doses of NXT007 at Days 1 and 15, and at trough concentrations during maintenance treatment every 4 weeks from Day 29. PD biomarkers included activated partial thromboplastin time (aPTT), FVIII-like activity (human chromogenic FVIII activity assay, Hyphen BioMed) and FXIa-triggered TG (Ceveron s100, Technoclone), and were measured in plasma samples collected during the pre-treatment and NXT007 treatment visits. To compare the PD effects of FVIII and NXT007, samples collected at Day 29 during NXT007 treatment, when loading doses were completed and maintenance dosing started, were compared with the samples taken 15 min after FVIII administration. In addition, FIX and FX concentrations, prothrombin time (PT), D-dimer, prothrombin fragment 1+2 (PF1+2) and fibrinogen were measured during NXT007 treatment. NXT007 plasma concentrations were measured using a validated immunoassay.

Results: Large variability was observed in the measured plasma FVIII activity after FVIII administration during the pre-treatment visit. The 15 min post-FVIII administration time point was used for comparing PD effects during NXT007 treatment, as that is when the highest FVIII activity was generally observed After the first NXT007 dose in all cohorts, aPT shortened and remained below normal range throughout the study. FVIII-like activity and TG peak height increased during NXT007 loading doses and were sustained from Day 29 onwards. PD effects increased with increasing NXT007 doses. The maximum effect on aPTT was reached at low, sub-therapeutic NXT007 concentrations. FVIII-like activity increased linearly with increasing NXT007 plasma concentrations and TG peak height increased following an Emax model approaching maximum effect at the highest concentrations.

In the lowest dose NXT007 cohort (Cohort 1), mean TG peak height at Day 29 was lower than the mean TG peak height 15 min post FVIII administration (pre-treatment visit). Mean TG peak heights in Cohorts 2 and 3 at Day 29 were close to the mean post-FVIII-infusion TG peak height at the pre-treatment visit, which was expected to achieve FVIII-like activity within the non-hemophilia range. No changes in FIX and FX concentrations, PT, D-dimer or fibrinogen were observed during NXT007 treatment, and increasing NXT007 concentrations had no impact on these markers. A slight increase in PF1+2 was seen, but was not considered to be of clinical significance.

Conclusions: PD markers were well correlated with NXT007 concentrations and demonstrated stable activity throughout the maintenance-dosing period, while safety biomarkers remained unaffected. In PwHA receiving prophylaxis with NXT007, the TG peak height during the steady state was in the non-hemophilia range and comparable to that obtained in participants with FVIII levels in the normal range.

Ex vivo evaluation of the procoagulant effect of NXT007 prophylaxis in people with Hemophilia A without factor VIII inhibitors: Phase I/II study (NXTAGE) (Abstract 3061, ASH 2025)

K. Nogami et al

Introduction: NXT007, an emicizumab-based next-generation bispecific antibody, mimics the cofactor function of activated factor VIII (FVIII) and has higher FVIII-mimetic activity and a longer half-life compared to emicizumab. A phase I/II clinical study of NXT007 in healthy volunteers and people with hemophilia A (PWHA) is currently ongoing (NXTAGE; jRCT2080224835). To investigate the pharmacodynamics and coagulation activity of NXT007, activated partial thromboplastin time (aPTT) and thrombin generation (TG) were measured in plasma from PwHA participating in multi-ascending-dose Part B of NXTAGE study.

Methods: Part B of NXTAGE study, consisted of four dosing cohorts, was conducted in PwHA without FVIII inhibitors who have not been treated with emicizumab (Shima et al., Res Pract Thromb Haemost 2025). aPTT was measured using Thrombocheck APTT-SLA and a CS-2400 automated blood coagulation analyzer (Sysmex Corporation). TG assay was performed using clinical repository plasma samples collected from the participants. TG peak height was measured by Medpace Reference Laboratories using the fully automated coagulation analyzer (Ceveron s100, Technoclone) with an activated factor XI trigger, which has been shown to be more robust and sensitive than tissue factor triggers (Waters et al., J Thromb Haemost 2015). Exploratory graphical analyses (for aPTT and TG) and an inhibitory maximum effect model analysis (for aPTT) were performed to investigate the response to different NXT007 plasma concentrations.

Results: aPTT was shortened in a plasma NXT007 concentration-dependent manner up to 5 ug/mL, at which FVIII-equivalent activity estimated based on factor IX-NXT007-factor X ternary complex concentration (Yoneyama et al., Blood 2022) was 28.8 IU/dL. At higher NXT007 concentrations, aPTT shortening was occurred only by a few seconds and appeared to have reached a plateau, where aPTT was below the lower limit of the reference range reported in the manufacturer's kit insert (24-32 seconds). This is likely because FVIIIa-mimetic bispecific antibodies do not require activation for function unlike FVIII, as known with emicizumab (Yoneyama et al., Expert Rev Clin Pharmacol 2023). The model-based analysis showed that NXT007 shortened aPTT to approximately 19 seconds at the maximum effect, and the NXT007 concentration causing 50% of the maximum effect (IC5o) was estimated to be 0.190 ug/mL. These values are lower than the mean aPTT at steady state (23.6 seconds) and the IC50 for aPTT shortening (1.1 ug/mL) reported in the Phase III HAVEN 1 study of emicizumab (Schmitt et al., Thromb Haemost 2021). Plasma samples for TG assay were collected from a total of 21 participants in Part B of NXTAGE study who consented to the clinical repository sample collection (n=10, 2, 4, and 5 for Cohorts B-1, B-2, B-3, and B-4, respectively). The TG peak height correlated with plasma NXT007 concentration up to approximately 25 ug/mL. Compared to the reference range established using 120 healthy donor samples, in which the FVIII activity was determined to be 29-133 IU/dL based on a chromogenic assay, the concentration-dependent normalization of TG peak height was observed starting at plasma NXT007 concentrations of ≥ 5 ug/mL. Given that the mean plasma NXT007 concentration was maintained at approximately 7 ug/mL in the maintenance dose period of Cohort B-2, in which the FVIII-equivalent activity of NXT007 was predicted to reach 40 IU/dL, the procoagulant effect of NXT007 was suggested to reach the non-hemophilia level at doses of Cohort B-2 and higher. Notably, the annualized bleed rate for treated bleeds in the maintenance dose period tended to be lower in participants with higher TG peak height. Non-bleeders in the maintenance dose period, consisting mostly of patients in Cohorts B-3 and B-4, tended to have a higher peak height within the reference range compared to bleeders.

Conclusions: These results suggest that NXT007 has the potential to provide a non-hemophilic range of coagulation activity in PwHA.

Next-generation FVIIIa-mimetic bispecific antibody NXT007: evaluation in preclinical models of hemostasis and thrombosis (Blood Advances 2025)

M. Locke et al

Abstract: NXT007 is a next-generation factor (F)VIIIa-mimetic bispecific antibody currently in Phase 1/2 trials. It was developed by optimizing the framework of emicizumab to achieve hemostatic normalization in people with hemophilia A (PwHA). Here, we provide a direct comparison of NXT007 with emicizumab, using a wide range of in vitro and in vivo preclinical models of hemostasis and thrombosis. NXT007 and emicizumab increased tissue factor (TF)-triggered peak height thrombin generation when spiked into HA-like (FVIII-neutralized) plasma, with NXT007 being more potent than emicizumab, peaking at lower concentrations and with higher maximum effect. NXT007 and

emicizumab delayed fibrinolysis in a dose-dependent manner, with NXT007 having ~20-fold more potent antifibrinolytic effect. Both bispecific antibodies corrected clotting times and kinetics of HA-like blood, measured by rotational thromboelastometry, with NXT007 being ~23-fold more potent. In collagen/TF-coated flow chambers perfused with HA-like blood at arterial shear rates, NXT007 and emicizumab increased fibrin deposition without increasing platelet adherence; maximum effect of NXT007 was greater than emicizumab and achieved at lower concentration. Following tail vein transection in HA mice, NXT007 was more potent than emicizumab in controlling bleeding. In a ferric chloride carotid injury model, administration of NXT007 and emicizumab at plasma concentrations ~20-200µg/mL had no effect on maximum blood flow reduction, indicating that they do not present a prothrombotic profile in this model. Overall, our data support the ongoing clinical evaluation of NXT007 and suggest that it has potential to substantially improve therapeutic efficacy for PwHA.

Bi8

Alternative AAV gene therapy for hemophilia A using expression of Bi8, a novel single-chain FVIII-mimetic antibody (Blood 2025)

V. Muczynski et al

Abstract: The recent approval of adeno-associated virus (AAV)-based gene therapies for hemophilia A (HA) represents a major advancement in the management of this X-linked bleeding disorder, offering multiyear bleed protection and improved quality of life over factor VIII (FVIII) replacement. However, challenges remain, including concerns over long-term durability of expression and the difficulty of packaging the oversized FVIII transgene into AAV vectors. To address these limitations, we developed AAV8-Bi8, a liver-directed gene therapy encoding Bi8, a novel 54.5-kilodalton FVIII-mimetic antibody. Bi8 is expressed as a compact, single-chain tandem, single-chain fragment variable, and is delivered via a 4.4-kilobase expression cassette packaged within AAV8 capsids, well within the vector packaging capacity. In vitro, Bi8 demonstrated FVIII-mimetic activity, and effectively corrected FVIII-deficient human plasma to levels comparable with emicizumab, the current market standard. In vivo, a single administration of AAV8-Bi8 in FVIII-deficient mice resulted in dose-dependent, durable expression of Bi8, complete phenotypic correction of bleeding, and therapeutic equivalence to both emicizumab-treated and wild-type animals. Importantly, no toxicity or antidrug antibody responses were observed. This approach, based on delivering FVIII-mimetic antibodies through AAV rather than truncated FVIII transgenes, could provide a more flexible and efficient platform for gene therapy in HA. AAV8-Bi8 has the potential to offer sustained, lifelong hemostatic control, including in patients who have developed inhibitors to FVIII.

Mim8

Mim8 prophylaxis in adults and adolescents with hemophilia A: 52-week efficacy and safety outcomes from the phase 3 FRONTIER2 study (Blood 2025)

S. Lentz et al

Introduction: Mim8 (denecimig) is a new-generation, bispecific antibody, activated factor VIII mimetic in clinical development for subcutaneous prophylaxis (PPX) for hemophilia A (HA) with or without inhibitors. The 26-week main phase of the phase 3 FRONTIER2 study (NCT05053139) demonstrated superiority of once-every-week (QW) and once-every-month (QM) Mim8 PPX in reducing annualized bleeding rates (ABRs) for treated bleeds versus on-demand therapy or prior clotting factor concentrate (CFC) PPX.

Aim: To assess 52-week efficacy and safety of Mim8 PPX in adults and adolescents (aged ≥12 years) with HA with or without inhibitors from the FRONTIER2 extension phase.

Methods: In the 26-week main phase, participants were randomized to Mim8 QW or QM, or continued on-demand standard-of-care treatment. Participants were grouped by prior treatment regimen: on-demand or CFC PPX. In the 26-week extension, all on-demand participants switched to Mim8 PPX (QW or QM); others continued their assigned regimen. Mim8 was administered using a tiered-dosing approach. Primary endpoint: number of treated bleeds; selected secondary endpoints: number of injection-site reactions (ISRs) and anti-Mim8 antibodies. ABR was estimated using a negative binomial regression model. Safety and immunogenicity were assessed. Ethics approval and informed consent were obtained.

Results: Of 281 randomized participants, 97% completed the main phase and 96% the extension. Mean (min; max) age at baseline was 32 (13;64) years for the pre-study on-demand group (n=61) and 31 (12;69) years for the pre-study CFC PPX group (n=220). In the pre-study CFC PPX group vs the pre-study on-demand group, there was a higher proportion of patients with severe HA (86% vs 77%) and lower proportion with inhibitors (2% vs 44%). This analysis includes 27 newly reported participants from China.

In the main phase, all participants who continued on-demand treatment (n=18) experienced treated bleeds. Estimated mean ABR (95% confidence interval [CI]) was 16.09 (11.21;23.09). All participants entered the extension, during which 88% (Mim8 QW, n=7/8) and 70% (Mim8 QM, n=7/10) had zero treated bleeds. Estimated mean ABRs (95% CI) were 0.67 (0.13;3.61) and 0.79 (0.19;3.33), respectively.

For participants previously treated on-demand: of those randomized to Mim8 QW, 86% (n=19/22) had zero treated bleeds in the main phase and 91% (n=19/21) in the extension, with estimated mean ABRs (95% CI) of 0.43 (0.17;1.07) and 0.45 (0.19;1.08), respectively; of those randomized to Mim8 QM, 91% (n=19/21) had zero treated bleeds in the main phase and 86% (n=18/21) in the extension, with estimated mean ABRs (95% CI) of 0.25 (0.08;0.76) and 0.25 (0.08;0.77), respectively.

For participants previously on CFC PPX: of those randomized to Mim8 QW, 67% (n=74/111) had zero treated bleeds in the main phase and 70% (n=73/104) in the extension, with estimated mean ABRs (95% CI) of 2.32 (1.35;3.99) and 1.28 (0.78;2.08), respectively; of those randomized to Mim8 QM, 63% (n=69/109) had zero treated bleeds in the main phase and 69% (n=74/108) in the extension, with estimated mean ABRs (95% CI) of 1.79 (1.22;2.63) and 1.54 (0.92;2.59), respectively.

Across main and extension phases, median ABR was 0 in all Mim8-treated arms. Adverse events (AEs) were reported in 74% (n=104) of Mim8 QW and 71% (n=100) of Mim8 QM participants. Most AEs were mild: 84% (399/475) of events with Mim8 QW and 82% (321/390) with Mim8 QM. Overall, ISRs occurred in 12% (n=17) of QW and 9% (n=12) of QM participants, accounting for 1.81% and

1.34% of injections, respectively. Overall, anti-Mim8 antibodies were detected in 21 (7%) recipients without clinical evidence of neutralizing activity; all were low (95%) or medium (5%) titer. No thromboembolic events, hypersensitivity reactions, or clinically relevant laboratory abnormalities were observed, including coagulation parameters.

Conclusion: Over 52 weeks, Mim8 QW and QM PPX provided sustained bleed protection in adults and adolescents with HA, with or without inhibitors, supporting its use as a long-term prophylactic option. During the extension, Mim8 was well tolerated, with infrequent ISRs, few serious AEs, no thromboembolic events or hypersensitivity reactions, and no anti-Mim8 antibodies with clinical impact. Participants completing FRONTIER2 are eligible for the open-label extension, FRONTIER4 (NCT05685238). Mim8 may offer an effective and convenient approach to reducing disease and treatment burden in this population.

Factor Replacement Therapies

Efanesoctocog alfa (Altuvoct, Altuviiio)

Clinical outcomes up to 4 years of once-weekly efanesoctocog alfa prophylaxis in previously treated adults, adolescents, and children with severe hemophilia A: Interim analysis of the Phase 3 XTEND-ed long-term extension study (Abstract 539, ASH 2025)

V. Susen et al

Introduction: Efanesoctocog alfa is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to decouple recombinant FVIII from endogenous von Willebrand factor. In the Phase 3 XTEND-1 (NCT04161495) and XTEND-Kids (NCT04759131) studies, once-weekly efanesoctocog alfa exhibited effective bleed protection, was well tolerated, providing FVIII activity within the normal to near-normal (>40%) range for 4 and 3 days, respectively, at steady state. We present the third interim analysis of the XTEND-ed (NCT04644575) long-term extension study examining the safety and efficacy of efanesoctocog alfa prophylaxis in patients with severe hemophilia A.

Methods: Participants who completed XTEND-1 (≥12 years) and XTEND-Kids (<12 years), could continue once-weekly 50 IU/kg efanesoctocog alfa prophylaxis in the ongoing, multicenter, open-label, long-term XTEND-ed study. The primary endpoint was the incidence of FVIII inhibitor development and secondary endpoints included annualized bleed rates (ABRs), efficacy for bleed treatment, and safety. Data cut: February 21, 2025.

Results: Among adults and adolescents, 146 participants rolled over from XTEND-1 to XTEND-ed baseline with a median (range) age of 37.0 (13.0–74.0) years. The median (range) treatment duration in XTEND-ed was 166.0 (14.1–192.7) weeks, comprising a median (range) of 167.0 (14.0–200.0) exposure days (EDs). The median (range) cumulative treatment duration from XTEND-1 baseline until XTEND-ed data cut was 212.2 (46.3–244.8) weeks, comprising a median (range) of 216.5 (47.0–254.0) EDs. No FVIII inhibitor development was observed. During XTEND-ed, the mean (SD) ABR for Day 1–Month 12 (n=146) was 0.70 (1.31), Months 12–24 (n=141) was 0.62 (1.23) and Months 24–36

(n=132) was 0.45 (1.24), with 96/146 (65.8%), 96/141 (68.1%), and 103/132 (78.0%) participants with zero bleeds, respectively. The mean (95% CI) model-based ABR for the efficacy period was 0.60 (0.47; 0.76) for overall treated bleeds, and 0.20 (0.15; 0.28) and 0.29 (0.22; 0.39) for spontaneous and traumatic bleeds, respectively. Of 252 treated bleeding episodes, 94.0% (237) were resolved with 1 efanesoctocog alfa injection; participants rated the response excellent/good for 87.8% (173/197) bleeds. The median (range) weekly efanesoctocog alfa consumption was 51.6 (39.4–58.9) IU/kg. In total, 126 participants (86.3%) experienced ≥1 treatment-emergent adverse event (TEAE), most commonly COVID-19 (26.7%), arthralgia (17.1%), influenza (15.1%), and nasopharyngitis (15.1%). Two participants had ≥1 treatment-related TEAE (facial paralysis and reduced FVIII levels); no treatment-related serious TEAEs were reported. TEAEs unrelated to study drug led to the death of 2 participants and treatment discontinuation in 3 participants.

Among children, 71 participants (<6 years, n=35; 6–<12 years, n=36) rolled over from XTEND-Kids to XTEND-ed, with the median (range) treatment duration of 116.7 (36.3–152.6) weeks, comprising a median (range) of 116.0 (11.0–153.0) EDs. The median (range) cumulative treatment duration from XTEND-Kids baseline until XTEND-ed data cut was 169.8 (88.2–204.7) weeks, with a median (range) of 171.0 (65.0–207.0) EDs. No FVIII inhibitors were observed. During XTEND-ed, the mean (SD) ABR evaluated for Day 1–Month 12 (n=71) was 0.68 (1.13) and Months 12–24 (n=62) was 0.49 (0.82), with 46/71 (64.8%) and 41/62 (66.1%) participants with zero bleeds, respectively. The mean (95% CI) model-based ABR was 0.64 (0.48; 0.85) for overall treated bleeds, and 0.08 (0.04; 0.15) and 0.44 (0.31; 0.62) for spontaneous and traumatic bleeds, respectively. Of 89 treated bleeding episodes, 91.0% (81) were resolved with 1 efanesoctocog alfa injection; participants rated the response excellent/good for 94.1% (64/68) bleeds. The median (range) weekly efanesoctocog alfa consumption was 54.0 (46.2–73.1) IU/kg. Overall, 60 (84.5%) participants experienced ≥1 TEAE; most commonly pyrexia (18.3%), upper respiratory tract infection (16.9%), arthralgia (15.5%), and cough (15.5%). Two participants had ≥1 treatment-related TEAE (asthma and post infusion pain and headache); no treatment-related serious TEAEs or treatment discontinuations were reported.

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

Rurioctocog Alfa Pegol

Real-world safety and effectiveness of rurioctocog alfa pegol in 338 patients with hemophilia A in South Korea: A postmarketing surveillance study (Thrombosis Research 2025)

J. Yoon Kim et al

Introduction: Rurioctocog alfa pegol is a recombinant coagulation factor VIII (FVIII) with an extended half-life versus the parent product. Limited real-world data exist on the treatment of hemophilia A with rurioctocog alfa pegol in South Korea. This postmarketing surveillance study assessed its safety and effectiveness in a real-world setting, according to Korean regulatory requirements.

Methods: In this prospective, multicenter study (NCT03824522), data were collected from medical records of patients, including children, with hemophilia A receiving rurioctocog alfa pegol as

standard clinical practice in South Korea. Safety (adverse events [AEs], adverse drug reactions [ADRs], and unexpected AEs/ADRs) and hemostatic effectiveness were analyzed.

Results: In total, 338 patients were included (mean age [range], 25.0 [1.0–61.0] years; children <12 years, *n* = 54 [16 %]; all had a history of FVIII treatment). AEs occurred in 20 (5.9 %) patients (unexpected AEs, *n* = 18 [5.3 %]; ADRs, *n* = 4 [1.2 %]; unexpected ADRs, *n* = 2 [0.6 %]; serious AEs, n = 4 [1.2 %]; serious ADRs, *n* = 0 [0.0 %]). Among children, AEs occurred in 1 (50 %) and 6 (11.5 %) patients aged <2 and ≥2 to <12 years, respectively. No new safety signals were observed. No bleeding events occurred in 239 (76.1 %) patients on prophylaxis. Hemostatic effectiveness was rated by physicians as excellent/good in most patients. Bleeding events were managed with 1–2 infusions. Treatment effectiveness was maintained in children during the study period. No patients developed inhibitor antibodies against rurioctocog alfa pegol.

Conclusion(s): Rurioctocog alfa pegol was effective in children and adults, with no new safety signals; most patients on prophylaxis experienced no bleeds during the study.

Gene Therapy

Factor IX-Padua AAV gene therapy in hemophilia B: phases 1/2 and 3 trials (Nature Medicine 2025)

F. Xue et al

Abstract: Gene therapy for hemophilia B with adeno-associated virus (AAV) vector has achieved great advances over the last decade. We previously conducted a pilot study demonstrating the safety and efficacy of AAV-factor IX (FIX) Padua gene therapy (BBM-H901) in ten male participants with hemophilia B. Here we report a single-arm dose-escalation phase 1/2 trial in 6 male participants and a multicentre phase 3 trial in 26 participants with hemophilia B in China. The phase 1/2 study tested a dose of 5 × 1012 vg kg-1 (n = 6), with primary endpoints assessing dose-limiting toxicities (DLT) and adverse events (AEs). The primary endpoint was met with no DLT observed in the 10 weeks postinfusion. The most common drug-related AEs were transaminitis (33.3%), and no grade 3 drug-related AE occurred within 52 weeks postintervention. The phase 3 study tested the 5 × 1012 vg kg-1 dose, as determined in the phase 1/2 study, in 26 patients. The primary endpoint evaluated the annualized bleeding rate (ABR) after gene therapy and secondary endpoints included vector-derived FIX:C, target joint and percentage of participants with zero bleeds postgene therapy. The study met its primary endpoint as the mean (95% confidence interval (CI)) ABR within 52 weeks after BBM-H901 infusion decreased to 0.60 (0.18-1.99), and the upper limit of the 95% CI (1.99) was lower than the predefined superiority margin of 5.0 (historical ABR assumed for patients receiving prophylactic FIX treatment in China). In the phase 3 trial, the most common drug-related AEs were transaminitis as well, and the vector-derived FIX:C had a mean of 41.9 (28.7) IU dl-1 at week 52. None of the participants had a target joint, and 80.8% of participants experienced zero bleeds during the 52-week follow-up. Our study supports the safety and efficacy of AAV-FIX Padua gene therapy in a large Chinese cohort.

Valoctocogene Roxaparvovec (Roctavian)

Estimated Long-Term Durability of Valoctocogene Roxaparvovec Treatment in Male patients with Severe Hemophilia A: An Extrapolation of Clinical Data (Advances in Therapy 2025)

S. Santos et al

Introduction: Valoctocogene roxaparvovec is a single administration gene therapy treatment that enables endogenous factor VIII (FVIII) production to prevent bleeding in people with severe hemophilia A. Valoctocogene roxaparvovec is associated with a higher probability of being bleed-free, improvements in annualized bleed rates, and improvements in health-related quality of life compared with FVIII prophylaxis. The economic value of valoctocogene roxaparvovec will be determined, in part, by the duration of time over which the treatment effect is maintained, and the consequences associated with loss of response. Therefore, this analysis aimed to estimate the long-term durability of valoctocogene roxaparvovec treatment effect by extrapolating pivotal and longer-term trial data (Phase 3 GENEr8-1 4- to 5-year and a Phase ½ study 7-year data) to inform decision-making.

Methods: Using data from the pivotal Phase 3 study GENEr8-1 and longer-term data from the 6E13 vg/kg cohort of Phase 1/2 Study 270–201, time to loss of response was analyzed within a time-to-event analysis framework. Loss of response was defined as a combination of: FVIII level decline < 5% and return to continuous prophylactic treatment and experiencing ≥ 2 treated bleed events in the previous 6 months at the time of return to prophylactic treatment.

Results: Data were available for 134 participants from GENEr8-1, and 7 participants from Study 270–201. The main analysis results for predicted median durability ranged from 11.0 to 17.0 years considering the three statistically best-fitting parametric distributions; considering five plausible distributions, results ranged from 8.1 to 25.6 years. In scenario analyses using different definitions of loss of response, the results were broadly similar, with median durability ranging from 7.2 to 31.8 years.

Conclusion: This analysis demonstrates the potential therapeutic benefit of valoctocogene roxaparvovec may be sustained beyond the follow-up period in existing clinical trials and across all parametric extrapolations and definitions analyzed, indicating that gene therapy may offer long-term benefits beyond what has been previously reported (i.e., 7 years).

Safety and efficacy of valoctocogene roxaparvovec with prophylactic glucocorticoids: 1-year results from the phase 3b, single-arm, open-label GENEr8-3 study (JTH 2025)

M. C. Ozelo et al

Background: Valoctocogene roxaparvovec, an adeno-associated virus vector that transfers a human factor (F)VIII (FVIII) coding sequence to hepatocytes, provides bleeding protection for people with severe hemophilia A.

Objectives: Determine the efficacy and safety of valoctocogene roxaparvovec with concomitant prophylactic glucocorticoids in the open-label, single-arm, phase 3b GENEr8-3 trial.

Methods: Participants with severe hemophilia A who were using hemophilia A prophylaxis received one 6 × 10^{13} vg/kg infusion of valoctocogene roxaparvovec concomitantly with daily prophylactic glucocorticoids (40 mg prednisolone equivalent/d weeks 0-8; taper to 5 mg/d weeks 9-19). The primary efficacy endpoint was change from baseline in FVIII activity (chromogenic substrate assay) at week 52. Secondary efficacy endpoints included annualized rate of FVIII use and annualized bleeding rate for treated bleeds. Safety was assessed by adverse events (AEs). Analysis populations were intent-to-treat (ITT; received valoctocogene roxaparvovec) for safety analyses and modified ITT (≥52 FVIII infusions in the year before dosing) for efficacy analyses.

Results: Overall, 22 participants with severe hemophilia A received valoctocogene roxaparvovec. In the modified ITT population (*n* = 21), mean week 52 FVIII activity increased from baseline (imputed as 1 IU/dL) to 16.1 IU/dL (SD, 22.4; *P* = .0057); posthemophilia A prophylaxis, mean treated annualized bleeding rate and mean annualized FVIII use decreased 67.1% and 91.6% from baseline, respectively (*P* < .05). The most common AE was alanine aminotransferase elevation (20/22 participants). Glucocorticoid-related AEs occurred in 19 of 22 participants. No participants discontinued the study.

Conclusion: Based on cross-trial comparisons, prophylactic glucocorticoids do not confer safety or efficacy benefits compared with reactive glucocorticoid regimens.

SPK-8011

Preclinical evaluation of SPK-8011QQ, an adeno-associated virus gene therapy for people with hemophilia A leveraging the dirloctocogene samoparvovec platform encoding an activated Protein C-resistant B-domain deleted factor VIII

N. Frey et al

Background: Gene therapies for hemophilia A (HA) offer the potential for durable factor (F)VIII expression as a curative treatment option. However, recent clinical programs and approved gene therapies expressing wild-type (WT) B-domain deleted (BDD) FVIII have faced challenges in reaching sufficient and/or durable FVIII levels. SPK-8011 QQ is an investigational adeno-associated virus (AAV) gene therapy that leverages the clinically evaluated safety and durability of the SPK-8011 (dirloctocogene samoparvovec) platform to introduce the enhanced-function FVIII-QQ variant (Wilhelm et al. Blood 2021). The optimized payload carries a two-amino acid change (R336Q; R562Q) that has 99.9% identity with the original transgene sequence. As a mode of action, the FVIII-QQ variant confers resistance to cleavage by the anticoagulant activated protein C (APC), thereby enhancing FVIII potency and hemostatic potential. This ongoing study evaluates the preclinical efficacy and safety of a surrogate vector for SPK-8011QQ *in vitro, ex vivo* and *in vivo*.

Methods: Surrogate AAV vectors for SPK-8011 QQ or SPK-8011 were administered intravenously to FVIII knock-out mice. Seven days post vector administration, plasma samples were collected and analyzed using APC-sensitive chromogenic substrate assay (CSA) and thrombin generation assay (TGA). APC-sensitive assays specifically evaluate FVIII function in the presence of APC, allowing for the differentiation of FVIII-QQ with enhanced potency from WT-BDD-FVIII, which standard assays cannot detect. Differences in FVIII-QQ potency and activity versus WT-BDD-FVIII were evaluated in murine samples using unpaired two-tailed t-test with Welch's correction. In addition, AAV-treated

mice were challenged in a 4mm tail-clip bleeding model 7 days post infusion. Concurrently, plasma samples were collected from the same mice to measure FVIII activity (FVIII:C) and antigen levels (FVIII:Ag).

Planned preclinical work to evaluate prothrombotic risks of the FVIII-QQ transgene will be conducted, whereby AAV-treated mice will be challenged with a 3.5% ferric chloride-induced carotid injury model and compared to mice infused with the control AAV (i.e. surrogate SPK-8011 vector). In addition, plasma samples from people with severe HA will be spiked with recombinant FVIII-QQ or WT-BDD-FVIII and evaluated in APC-sensitive CSA and TGA. Results from ongoing preclinical work will be presented once data are available.

Results: Analysis of murine ex vivo samples in APC-sensitive assays resulted in residual FVIII activity increasing by 30% in the CSA (p=0.03), and 24% in the TGA (p=0.12), for the surrogate SPK-8011 QQ group compared with the control vector. In the tail-clip model, at comparable FVIII activity levels, mice treated with surrogate SPK-8011 QQ exhibited significantly reduced bleeding times and blood loss compared with those treated with surrogate SPK-8011. Analysis of blood loss as a function of FVIII:C demonstrated an approximately 9-fold increase in potency for surrogate SPK-8011QQ (EC50: 12.2% FVIII:C) relative to the control vector (EC50: 112.3% FVIII:C).

The prothrombotic risk assessment in the carotid injury model will be presented once readouts are available. Similarly, findings in severe HA plasma samples spiked with recombinant FVIII-QQ and WT-BDD-FVIII will be discussed.

Conclusions: Surrogate SPK-8011 QQ, which leverages the previously clinically evaluated SPK-8011 (dirloctocogene samoparvovec) platform to introduce FVIII-QQ, demonstrates markedly enhanced hemostatic potency under APC-sensitive conditions in ex vivo and in vivo mouse models. Furthering the learnings from the safety and durability of the SPK-8011 platform, our preclinical data collected to date support the ongoing evaluation of SPK-8011 QQ, which aims to optimize FVIII potency and hemostatic potential.

Haemophilia B

Replacement therapies

Orthopaedic Surgery Outcomes in Patients With Haemophilia A or B Treated With Extended Half-Life Recombinant Factor VIII and IX Fc Fusion Proteins: A Multicentre Prospective Study (Haemophilia 2025)

L. P. Solimeno et al

Introduction: Haemophilia A and B are hereditary bleeding disorders that require multidisciplinary perioperative management. Data on orthopaedic surgery outcomes with extended-half-life (EHL) recombinant Fc-fusion factor VIII (rFVIIIFc) and factor IX (rFIXFc) products remain limited.

Aims: To evaluate the efficacy of EHL rFVIIIFc or rFIXFc in major orthopaedic surgery, focusing on haemostasis, safety and factor consumption.

Methods: This prospective study involved persons with haemophilia A or B treated with rFVIIIFc or rFIXFc undergoing orthopaedic surgery.

Results: Twenty major orthopaedic surgeries (2018–2023) were included in 19 persons with severe or moderate haemophilia A (n = 14) or B (n = 5), median age 46 years (range 26–60). Procedures included arthroplasty, arthrodesis, arthroscopic synovectomy, prosthetic revision of the knee or ankle, and removal of a femur fracture fixation device. Median hospital stay was 7 days (range 2–18). Median cumulative factor consumption was 300 and 388 IU/kg for haemophilia A and B, respectively. Haemostatic efficacy was rated as 'good' in 95% (n = 18) of cases, 'poor' in 5% (n = 1), and not documented in one case. Median haemoglobin (Hb) change was –2.0 g/dL (range –4.6 to +0.5); no transfusions were required. Complications were reported in 45% (n = 9) of cases (anaemia 40%; blood loss 5%) and managed with oral supplementation of iron and folates. No adverse events related to rFVIIIFc or rFIXFc administration were observed.

Conclusions: RFVIIIFc and rFIXFc provide effective haemostasis during orthopaedic surgery in patients with haemophilia A and B, with a favourable safety profile. Further multicentre studies are warranted to confirm these results and refine perioperative management guidelines.

HAEMFIX: Impact of Switching From SHL-FIX to EHL-FIX in Patients With Haemophilia B (Haemophilia 2025)

J. Lonardi et al

Introduction: Haemophilia B is an X-linked recessive bleeding disorder caused by coagulation factor IX (FIX) deficiency. Treatment involves intravenous replacement of FIX. Recently, extended half-life (EHL) FIX products have been introduced alongside standard half-life (SHL) products to optimize therapy.

Aim: This study evaluated bleeding rates, joint health, factor consumption, dosage, and health-related quality of life (HRQoL) in patients switching from SHL- to EHL-FIX products, as well as in those exclusively treated with EHL-FIX.

Methods: Retrospective data from the medical records of 37 children with haemophilia B treated between 2010 and 2023 at two German Haemophilia Care Centres were analysed. HRQoL was assessed cross-sectionally using haemophilia-specific and generic questionnaires.

Results: Twenty-seven patients (median age: 12 years, range 2–19 years) switched from SHL- to EHL-FIX, while 10 received EHL-FIX from the start of prophylaxis. The mean annual bleeding rate (ABR) improved from 6.01 ± 7.01 (SHL) to 2.85 ± 3.42 (EHL). Factor consumption (159,577.8 ± 99,817.9 IU/year), dosage (118.9 ± 50.3 IU/kg/week) and infusion frequency (145 ± 35.6 infusions/year) decreased after switching (100,247.7 ± 46,268.6 IU/year; 56.4 ± 23.7 IU/kg/week; 55.1 ± 9.8 infusions/year). HRQoL improved in both self-reports and parent reports. No severe adverse events occurred.

Conclusion: Switching from SHL-FIX to EHL-FIX in children with haemophilia B is safe and may improve outcomes by reducing bleeding rates, infusion frequency, and factor consumption while enhancing joint health and HRQoL.

Gene Therapy

Etranacogene dezaparvovec (Hemgenix)

Final Analysis of a Study of Etranacogene Dezaparvovec for Hemophilia B (NEJM 2025)

S. W. Pipe et al

Background: Prophylactic treatment for hemophilia B necessitates lifelong, regular intravenous factor IX infusions. Gene therapy offers the possibility of a single-dose treatment that produces durable endogenous factor IX expression and disease control. Etranacogene dezaparvovec comprises an adeno-associated virus serotype 5 (AAV5) vector and the highly active Padua factor IX variant. The primary analysis of this study showed that etranacogene dezaparvovec reduced annualized bleeding rates and adverse events were mainly of low-grade severity. Final data from 5 years of follow-up are now available.

Methods: In this open-label, phase 3 study, after a lead-in period (≥6 months) of factor IX prophylaxis, we administered a single infusion of etranacogene dezaparvovec in men with hemophilia B (factor IX activity level, ≤2 IU per deciliter), regardless of preexisting AAV5 neutralizing antibodies. The prespecified 5-year analyses included adjusted annualized bleeding rates (difference between the post-treatment period of months 7 through 60 after gene therapy and the lead-in period), factor IX expression, and safety outcomes.

Results: In the full analysis population (54 participants), the adjusted annualized bleeding rate for all bleeding events was 4.16 during the lead-in period and 1.52 during months 7 through 60 after gene therapy, a reduction of 63% (95% confidence interval, 24 to 82). During the 5-year follow-up period, endogenous factor IX expression remained stable; at 5 years, the mean (±SD) factor IX activity level was 36.1±15.7 IU per deciliter and the mean exogenous factor IX consumption for routine prophylaxis and treatment of bleeding events had decreased by 96%, from 257,339 IU per year during the lead-in period to 10,924 IU per year during months 7 through 60 after gene therapy. Efficacy did not differ substantially between participants with and those without AAV5 neutralizing antibodies at baseline. Adverse events that were possibly related to treatment were rare after month 6.

Conclusions: Sustained endogenous factor IX expression and low annualized bleeding rates over a 5-year period were observed after an infusion of etranacogene dezaparvovec.

Natural history of preexisting AAV5 antibodies in adults with hemophilia B during the lead-in of the etranacogene dezaparvovec phase 3 study (Molecular Therapy 2025)

R. Klamroth et al

Abstract: esting for binding or neutralizing antibodies (NAbs) to adeno-associated virus (AAV) is part of the laboratory assessment of people with hemophilia considering AAV-based gene therapy. We evaluated the natural history of NAb titers to AAV serotype 5 (AAV5) in adult males ≥18 years old with hemophilia B (factor IX ≤ 2%) during the lead-in period of a phase 3 trial prior to the infusion of etranacogene dezaparvovec to characterize NAb in addition to immunoglobulin G (IgG) and immunoglobulin M (IgM) anti-AAV5 binding antibody changes over time. At screening, 48% (32/67)

of enrolled participants had detectable NAbs (NAb+) with a median titer of 58 (range: 9–3,440). Participant-specific lead-in periods differed and included discontinuers (median duration: 240 days; range: 1–360). The median intra-participant coefficient of variation of NAb titer over time was 25% (range: 2%–154%). NAb seropositivity was associated with older age (p = 0.0065). For participants with detectable anti-AAV5 NAbs and IgG, there was a high correlation of titers at each visit (median r = 0.96; range: 0.92–0.99). IgM anti-AAV5 antibodies were detectable in only 9% of participants, and seroconversion was infrequent. In conclusion, AAV5 NAb test results were consistent over 6 months, which informs the timing of NAb screening when considering gene therapy for hemophilia B.

Evaluation of One-Stage Assays for the Monitoring of Recombinant Human Factor IX Padua Activity After Etranacogene Dezaparvovec Gene Therapy (Haemophilia 2025)

J. Astermak et al

Introduction: Accurate and reproducible measures of factor activity are required to guide clinical decision-making following gene therapy for haemophilia B (HB). Highly significant discrepancies have been observed in measurements of various factor IX (FIX) concentrates that carry molecular modifications to extend their half-life, arguing for the need for careful analysis of new HB treatment modalities with respect to FIX assay performance.

Aim: To further characterise variability in FIX activity measured using different one-stage assays (OSAs) and chromogenic assays (CAs) in patients with HB receiving gene therapy utilising the FIX Padua variant and to assess whether assay differences were due to the FIX-Padua variant.

Methods: FIX activity was assessed centrally (OSA and CA) and locally (OSA only) using plasma samples collected from a phase 2b and phase 3 study of etranacogene dezaparvovec and in an in vitro study of wild-type (wt) recombinant human FIX (rhFIX) and rhFIX-Padua.

Results: Lower CA than OSA FIX activity for plasma samples from the phase 3 trial was observed (CA:OSA ratio: 0.408 [±0.049]–0.547 [±0.062]). Local OSA:central OSA FIX activity ratios were 0.789 (±0.314)–1.021 (±0.159). Local OSA:central OSA FIX activity ratios across methods and/or reagents were 0.81 (±0.02)–1.28 (±0.04) for rhFIX-wt-spiked samples and 0.67 (±0.02)–1.13 (±0.09) for rhFIX-Padua-spiked samples.

Conclusion: FIX activity differences between central and local OSAs were modest; similar differences were observed in vitro with rhFIX-wt versus rhFIX-Padua. Commonly available OSAs can be used to monitor patients post-etranacogene dezaparvovec administration; we recommend using the same assay platform throughout the post-treatment period.

Elevation of liver health biomarkers before and after etranacogene dezaparvovec gene therapy in hemophilia B: Associations with long-term clinical outcomes (Abstract 6093, ASH 2025)

W. Miesbach et al

Introduction: Gene therapy with etranacogene dezaparvovec has emerged as a transformative treatment for individuals with hemophilia B, offering sustained endogenous factor IX (FIX) expression and reduced bleeding rates. Due to etranacogene dezaparvovec being a liver-targeting adeno-associated virus-mediated gene therapy, pre-existing hepatic conditions or post-treatment liver-

related events may influence therapeutic outcomes and are areas of clinical interest. This analysis presents 4-year follow-up data from participants treated with etranacogene dezaparvovec, stratified by liver-related clinical characteristics, particularly alanine aminotransferase (ALT) elevation, to explore the relationship between hepatic status and long-term efficacy, safety, and durability of FIX expression.

Methods: HOPE-B (NCT03569891) was a single-arm phase 3 study involving adult males with hemophilia B (FIX activity ≤2%). Liver-related exclusion criteria included serum liver chemistries >2 x upper limit of normal

(ULN); active hepatitis B (HBV) or C (HCV) infection or HIV replication; and advanced liver fibrosis. Fifty-four participants received a single dose of 2 x 1013 genome copies/kg etranacogene dezaparvovec after a ≥6-month lead-in period on FIX concentrate prophylaxis. Participants were grouped by (1) pre-dose ALT/aspartate aminotransferase (AST) >1 to <2x ULN (pre-ALT+/-), (2) post-dose ALT elevations requiring corticosteroids (CS) (ALT/CS+/-), and (3) ALT elevations within 18 weeks post-dose regardless of CS use (post-ALT+/-), and for these, FIX activity and adjusted annualized bleeding rate (ABR) were studied.

Additionally, late confirmed ALT elevations (ALT >ULN in 2 consecutive samples during months [M]7-48) and treatment-related ALT elevations (ALT >ULN) are reported.

Results: Eight participants (14.8%) had an ALT/AST >1 to ≤2x ULN prior to dosing. Meantstandard deviation (SD) FIX activity at Y4 in pre-ALT+ and pre-ALT- was 32.6+21.7% and 38.4t15.6%, respectively. Both groups showed ABR reductions: pre-ALT+ from 2.6 (95% CI 1.2-5.4) during lead-in to 1.32 (0.4-4.8) over the first year following stable expression (M7-18), maintained at 0.4 (0.1-1.5) during Y4; pre-ALT-: lead-in: 4.5 (3.4-5.9), M7-18: 1.5 (0.8-2.9), Y4: 0.4 (0.2-0.7).

Nine participants (16.7%) experienced ALT elevations consistent with vector-associated liver inflammation beginning weeks 3-7 post-infusion, prompting oral CS therapy. Mean FIX activity, stably expressed over 48 months follow-up (M6: 18.7+11.1%; Y4: 19.4+12.6%) was lower in ALT/CS+ participants compared to the ALT/CS- (M6: 43.3+17.2%; Y4: 40.6+15.4%). Despite this, both groups had substantial ABR reductions: from 4.3 (3.2-5.8) during lead-in to 1.8 (0.9-3.8) in M7-18 and 0.33 (0.2-0.6) during Y4 in the ALT/CS- group; from 3.8 (2.3-6.0) during lead-in to 0.82 (0.3-2.4) in M7-18 and 0.56 (0.2-1.3) during Y4 in the ALT/CS+ group. Including two additional participants with ALT elevations (week 11 and 18) for whom no post-ALT CS were initiated did not alter this pattern.

Confirmed ALT increase beyond M6 after treatment was observed in six (11.1%) participants at 1 to ≤2.5 x ULN; all but one had ALT 1 to ≤2 x ULN during lead-in, including two from the ALT/CS group. Although the one participant without baseline ALT elevation had a history of HIV, HBV, and HCV, the late ALT elevation was assessed by the investigator as alcohol related. Late increases in ALT did not affect FIX activity in these participants.

Treatment-related transaminitis following M6 occurred in only one participant (ALT 1.2 ULN) at a single timepoint in Y4, which resolved without sequelae.

Conclusion: Following a single dose of etranacogene dezaparvovec, participants with pre-dose elevated ALT/AST or post-dose (CS-treated) ALT elevation maintained FIX expression (albeit lower

in the ALT/CS group) and had similar bleed reduction up to 4 years post-dose, compared to those without ALT elevations.

Long-term liver deterioration following liver-targeted gene therapy was not observed over four years, not even in those identified as potentially at risk due to subacute liver inflammation following vector delivery.

These findings demonstrate that in cases of mild ALT/AST elevation prior to treatment, and/or with appropriate surveillance and management of ALT increase post-treatment, etranacogene dezaparvovec achieves hemostatic protection similar to that observed in individuals without ALT elevation, with comparable long-term safety.

Bypassing Agents

In vitro comparison of eptacog beta and eptacog alfa with antithrombin lowering (simulated fitusiran) using thrombin generation assay (Abstract 1295, ASH 2025)

S. Zaheer et al

Introduction: Eptacog beta, an FDA approved bypassing agent for the treatment of bleeds in patients with hemophilia A and B with inhibitors differs from eptacog alfa in its glycosylation profiles and platelet binding properties. Fitusiran, a non-factor therapy that suppresses antithrombin (AT) production was recently approved for prophylaxis in hemophilia A and B, with or without inhibitors. For persons with hemophilia and inhibitors, breakthrough bleeds on fitusiran prophylaxis would require treatment with a bypassing agent. In fitusiran clinic trials, eptacog alfa was used at reduced dosing (45ug/kg) for bleed management. To date, the combined effect of eptacog beta and fitusiran on in vitro thrombin generation (TG) has not been described. Our study aims to characterize the impact of eptacog beta (eB) and AT lowering (to mimic fitusiran) on TG parameters and compare to that of eptacog alfa (eA).

Methods: Thrombin generation assay with a tissue factor trigger was used to evaluate peak (nM) and endogenous thrombin potential (ETP (nM*min)) in pooled FVIII deficient plasma spiked with concentrations of eA ranging from 0-2 ug/mL (0-120 ug/kg), or eB ranging from 0-3.22 ug/mL (0-300 ug/kg). AT levels (15 - 92%) were achieved via an anti-human AT antibody. AT activity was measured by a chromogenic assay. Pooled normal plasma (PNP) was used as control.

Results: TG parameters of PNP were peak (71.2-154.8) and ETP (879.08 -1472.43).

TG parameters that exceeded the upper limit of the assay were noted at the following combinations:

15% AT with ≥ 0.17ug/mL (25 ug/kg) eB; ≥ 0.25ug/mL (15 ug/kg) of eA

20% AT with ≥ 0.45 ug/mL (50 ug/kg) eB; ≥ 0.25 ug/mL (15 ug/kg) eA

25% AT with ≥ 1.28 ug/mL (125 ug/kg) eB; ≥ 0.75 ug/mL (45 ug/kg) eA

30% AT with ≥ 2.44 ug/mL (225 ug/kg) eB; ≥ 1.0 ug/mL (60 ug/kg) eA

35% AT with ≥ 2 ug/mL (120 ug/kg) eA

High TG parameters were noted at the following combinations:

20% AT with eB: 0.17ug/mL (25 ug/kg) [peak 174, ETP 3383] and 0.28ug/mL (35 ug/kg) [peak 181, ETP 3567]

25% AT with eB: 0.17ug/mL (25 ug/kg) [peak 164, ETP 3331]; 0.28 ug/mL (35ug/kg) [peak 174, ETP 3461]; 0.45 pg/mL (50 pg/kg) [peak of 177.9, ETP of 3545]; 0.57 ug/mL (75 ug/kg) [peak 177.37, ETP of 3705];

25% AT with eA: 0.25 ug/mL (15 ug/kg) [peak 176.85, ETP 3357]; 0.5 ug/mL (30 ug/kg) [peak 177.27, ETP 3961];

30% AT with eB: 0.28 ug/mL (35ug/kg) [peak 165, ETP 3280]; 0.45 ug/mL (50 ug/kg) [peak 166.14, ETP 34171; 0.57 ug/mL (75 ug/kg) [peak 175.24, ETP 3616]; 1.28 ug/mL (125 ug/kg) [peak 179, ETP 3651]; 1.56 ug/mL (150 ug/kg) [peak 181, of 3715]

30% with eA: 0.25 ug/mL (15 ug/kg) [peak
165, ETP 3265]; 0.5ug/mL (30 ug/kg) [peak 178.34, ETP 3795]; 0.75 ug/mL (45 ug/kg) [peak 179, ETP 4010]

35% AT with eB: 0.45 ug/mL (50 ug/kg) [peak 158, ETP 3286]; 0.57 ug/mL (75 ug/kg) [peak 159, ETP 3523]; 1.28 ug/mL (125 ug/kg) [peak 168, ETP of 3625]; 1.56 ug/mL (150 ug/kg) [peak 167, ETP 3672]; 2.44 4g/mL (225 kg/kg) [peak 171, ETP 3788]; 3.22 ug/mL (300 4g/kg) [peak 176, ETP 3908]

35% with eA: 0.25 ug/mL (15 ug/kg) [peak 155, ETP of 3173]; 0.5ug/mL (30 ug/kg) [peak 166, ETP 3704]; 0.75 ug/mL (45 ug/kg) [peak 175, ETP 3823]; 1.0 ug/mL (60 ug/kg) [peak 177, ETP 4077]; 1.5 ug/mL (90 ug/kg) [peak 181, ETP 4249]

Normal TG were seen at the following combinations:

30% AT with: 0.17 ug/mL (25 ug/kg) eB [peak 153, ETP 3184]

35% AT with: 0.17 ug/mL (25 ug/kg) eB [peak 146, ETP 3045]; 0.28 ug/mL (35ug/kg) eB [peak 149, ETP 3120}

AT levels ≥40 % with all doses of eA and eB resulted in normal or slightly above normal TG parameters.

Conclusions: These results demonstrate that in vitro both eptacog beta and eptacog alfa similarly increase TG when AT levels are reduced to fitusiran target ranges. Eptacog alfa doses of 45ug/kg, used to treat bleeds in patients on fitusiran, had similar TG parameters to the 75ug/kg and 125ug/kg doses of eptacog beta. This data provides *in vitro* proof of concept supporting the use of eptacog beta for the treatment of breakthrough bleeds of patients on fitusiran prophylaxis. The clinical implications of the amplified in vitro TG remain to be seen, and human *in vivo* studies are needed to support patient bleed management guidelines.

Rebalancing Therapies

Concizumab (brand name Alhemo)

Concizumab plasma concentration measurements for personalized dose adjustment in patients with Hemophilia A/B with and without inhibitors: Data from the Phase 3 explorer7 and explorer8 studies (Abstract 3070, ASH 2025)

H. Eichler et al

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

Aim: Describe the observed and modelled pharmacokinetics (PK) and bleeding outcomes from one-time concizumab dose adjustments in phase 3 concizumab studies.

Methods: In two prospective, multicenter, open-label, phase 3 concizumab studies, explorer7 (patients with inhibitors; NCT04083781) and explorer8 (patients without inhibitors; NCT04082429), male patients aged ≥12 years were randomized 1:2 to no prophylaxis (arm 1) or concizumab prophylaxis (arm 2) or allocated to non-randomized concizumab prophylaxis (arms 3 and 4). Following a study pause due to non-fatal thromboembolic events in 3 patients receiving concizumab, a revised dosing regimen was implemented with a 1.0 mg/kg loading dose on the first day of treatment, followed by an initial daily dose of 0.20 mg/kg. At week 4, concizumab plasma concentrations were measured with a clinical trial enzyme-linked immunosorbent assay for potential one-time dose adjustments to set the maintenance dose. The dose was increased to 0.25 mg/kg if concizumab plasma concentration was <200 ng/mL, decreased to 0.15 mg/kg if >4,000 ng/mL, or maintained at 0.20 mg/kg if between 200-4,000 ng/mL. Population PK modeling was used to simulate concizumab exposure and response. Efficacy outcomes based on dose adjustments from the primary analysis (explorer7) or confirmatory analysis (explorer8) cut-offs are presented.

Results: A total of 281 patients were assigned to one of four arms in explorer7 and explorer8 (62.3% White, 28.1% Asian, 4.6% Black/African American, 2.1% American Indian/Alaska native, 2.5% not reported, 0.4% other). Concizumab plasma concentration was measured in 218 of 226 concizumab-exposed patients in arms 2-4; 8 patients withdrew before maintenance doses were reported. Of the 218 patients measured, 153 (70.2%) continued with a maintenance dose of 0.20 mg/kg, 55 (25.2%) patients adjusted to 0.25 mg/kg and 10 (4.6%) patients adjusted to 0.15 mg/kg.

The majority of patients (70.2%) had concizumab plasma concentrations between 200-4,000 ng/mL at week 4 and continued with maintenance dose at 0.20 mg/kg; mean concizumab plasma concentration in this group were 629 ng/mL and 608 ng/mL at week 4 and week 12, respectively. The proportion of patients with concizumab plasma concentrations <200 ng/mL at week 4 and adjusted to 0.25 mg/kg was 25.2%, consistent with the population model prediction of 21%. After dose adjustment to 0.25 mg/kg, the mean concizumab plasma concentration in the <200 ng/mL group increased from 119 ng/mL to 296 ng/mL from week 4 to week 12. The proportion of patients with concizumab plasma concentrations >4,000 ng/mL at week 4 and adjusted to 0.15 mg/kg was

4.6%, lower than the model prediction of approximately 10%. After dose adjustment to 0.15 mg/kg, the mean concizumab plasma concentration decreased from 5,525 ng/mL to 766 ng/mL from week 4 to week 12. Post-dose adjustment concizumab plasma concentrations aligned with modelled predictions.

Based on simulated efficacy outcomes in the <200 ng/mL group, increasing the daily maintenance dose to 0.25 mg/kg would reduce the predicted annualized bleeding rate (ABR). Consistent with modelled predictions, observed mean ABR within the <200 ng/mL group was lower after dose adjustment vs before dose adjustment: 3.8 (standard deviation [SD]: 8.2; mean observation period 262 days) vs 7.2 (SD: 10.4; mean observation period 64 days), respectively. Mean ABR in the <200 ng/mL group after dose adjustment was similar to the 200-4,000 ng/mL group (3.1; SD: 6.5; mean observation period 287 days). For patients with >4,000 ng/mL plasma concizumab, observed mean ABR after dose adjustment was 3.8 (SD: 4.8; mean observation period 340 days), similar to the 200-4,000 ng/mL group (3.1; SD: 6.5; mean observation period 287 days).

Conclusions: These findings support the use of concizumab plasma concentration-guided dose adjustments to optimize prophylaxis in patients with hemophilia A or B, with or without inhibitors. Exposure-response analyses confirmed the validity of the selected lower (200 ng/mL) and upper (4,000 ng/mL) limits of concizumab plasma concentration and showed that dose adjustments can effectively personalize therapy to reduce bleeding rates.

Marstacimab

Marstacimab prophylaxis in participants with Hemophilia A or B with inhibitors: Results from the Phase 3 BASIS trial (Abstract 306, ASH 2025)

D. Matino et al

Abstract: Marstacimab is a monoclonal antibody that inhibits tissue factor pathway inhibitor to enhance thrombin generation and restore hemostasis in participants (pts) with hemophilia A (HA) or hemophilia B (HB). The phase 3 BASIS study (NCT03938792) evaluated the safety and efficacy of marstacimab in adults and adolescents with severe HA (factor VIII <1%) or moderately severe to severe HB (factor IX ≤2%), with or without inhibitors. Marstacimab was approved for prophylactic use in individuals with HA or HB without inhibitors. Here, we present results of the BASIS study in pts with inhibitors.

Methods: This open-label, single-arm study enrolled males aged ≥12 to <75 years with current or historical high-titer inhibitors (≥5 BU/mL). After a 6-month observational phase (OP) on bypassing agents (on-demand [OD] or routine prophylaxis [RP]), pts received a subcutaneous loading dose of marstacimab 300 mg followed by 150 mg once weekly (QW) during the 12-month active treatment phase (ATP). The primary endpoint was annualized bleeding rate (ABR) for treated bleeds during marstacimab prophylaxis vs prior OD therapy with bypassing agents. Secondary endpoints included ABR for specific bleed types and patient-reported health-related quality of life (HRQOL). Safety, including the incidence and severity of adverse events (AEs) and immunogenicity, was evaluated in all dosed pts.

Results: Sixty pts (44 adults, 16 adolescents) with HA (n=47) or HB (n=13) with inhibitors entered the OP (OD: n=57; RP: n=3), with 51 transitioning to the ATP (OD: n=48; RP: n=3). Median age was 23 (range 12-75) years. Most pts were Asian (53.3%) or White (31.7%). At baseline, 71.9% of OD pts and 66.7% of RP pts had ≥1 target joint. Median marstacimab treatment duration was 364 (range, 259-406) days. Marstacimab reduced the mean ABR for treated bleeds from 19.78 (95% CI: 16.12, 24.27) in the OP to 1.39 (95% CI: 0.85, 2.29) in the ATP, demonstrating superiority of marstacimab over OD therapy (estimated ABR ratio, 0.07 [95% CI: 0.042, 0.118]; 2-sided P<0.0001). Results were consistent by hemophilia type, age, and geographic subgroup. For all bleed types, mean ABR was consistently superior with marstacimab vs OD in the OP (joint: 1.10 vs 15.15; spontaneous: 0.87 vs 15.27; target joint: 0.79 vs 6.42; total [treated and untreated]: 4.36 vs 27.29; estimated ABR ratio, ≤0.16; 2-sided P≤0.0001 for all bleed types). Marstacimab also demonstrated superiority vs OD therapy in all patient-reported HRQOL endpoints, except EQ-visual analog scale (VAS). After 6 months in the ATP, pts reported significantly greater improvements in Haem-A-QoL Physical Health domain (estimated median difference vs OP, - 25.9 [95% CI: -37.5, - 14.2]; 2-sided P<0.0001), Haem-A-QoL total score (estimated median difference, - 13.5 [95% CI: -19.8, - 7.2]; 2-sided P<0.0001), and EQ-5D-5L index score (estimated median difference, 0.1043 [95% CI: 0.0060, 0.2027]; 2-sided P=0.0377). During the ATP, 38 (74.5%) pts reported AEs, mostly mild or moderate; the most frequent were COVID-19 (21.6%), upper respiratory tract infection (15.7%), fibrin D-dimer increased (9.8%), and headache (9.8%). A total of 5 pts reported serious AEs (SAES) during the OP.One pt reported an SAE (treatment-related skin rash [grade 3], resolved at follow-up) during the ATP, which led to study discontinuation. Ten pts had their marstacimab dose temporarily discontinued or reduced due to an AE, most commonly COVID-19 (7 pts). Antidrug antibodies (ADAs) were detected in 10/51 (19.6%) pts; titers were low and 9/10 cases resolved by end of study. ADA status had no impact on efficacy or safety endpoints. Neutralizing antibodies were detected in 2 pts; titers were low and antibodies were transient and resolved by end of study. No deaths or thrombotic events were reported.

Conclusion: In pts with HA or HB and inhibitors, subcutaneous marstacimab QW significantly reduced ABR for all bleeding related endpoints vs prior OD therapy and improved HRQOL. Marstacima demonstrated a favorable safety profile, consistent with the noninhibitor cohort and earlier studies.

Management of breakthrough bleeds in participants with hemophilia A or B without inhibitors receiving marstacimab prophylaxis in the phase 3 BASIS study (Abstract 3066, ASH 2025)

D. Matino et al

Background: Marstacimab is a monoclonal antibody that targets the tissue factor pathway inhibitor to rebalance hemostasis. It is approved for prophylaxis in patients with hemophilia A (HA) or B (HB) without inhibitors. The pivotal phase 3 BASIS study (NCT03938792) demonstrated marstacimab was effective in reducing treated bleeds vs prior on-demand (OD) or routine prophylaxis (RP) therapy in participants (pts) with severe HA (FVIII < 1%) or moderately severe to severe HB (FIX ≤2%) without inhibitors. We aimed to assess the management of breakthrough bleeding episodes in pts who received concomitant factor replacement therapy (FRT) and weekly (QW) marstacimab in BASIS.

Methods: BASIS enrolled male pts aged ≥12 to <75 years. Results are reported for the noninhibitor cohort. Pts entered a 6-month observational phase (OP) and received prescribed FRT (OD or RP) before entering the 12-month active treatment phase (ATP) to receive a single dose of 300 mg

marstacimab (2×150 mg subcutaneous [SC]) followed by 150 mg SC QW. To manage breakthrough bleeds, pts could take their prescribed FRT at the lowest effective dose, determined by each investigator per the approved product label. FRT dose, date, and time of infusions and FRT product were recorded in an electronic diary; the type of product (plasma-derived [pd], recombinant standard half-life [SHL], or recombinant extended half-life [EHL]) was determined. An acute treated bleed was defined as a bleeding event treated with episodic FRT within 48 hours of the bleed starting.

Results: Of 128 pts (HA: n=101; 78.9%; HB: n=27; 21.1%) who entered the OP, 116 received marstacimab prophylaxis in the 12-month ATP. At baseline, median age was 30.0 (range 13-66) years, and most were White (50.8%) or Asian (47.7%); 36 (97.3%) and 53 (58.2%) pts in the OD and RP groups, respectively, had ≥1 target joint. The median (range) marstacimab treatment duration was 12.1 months for both the OD (11.5-13.1 months) and RP (0.9-12.8 months) groups. In all, 75 (64.6%) pts experienced 453 acute bleeding events in the ATP, which were treated with 555 FRT infusions (OD: 125; RP: 430). Most acute breakthrough bleeds (OD: 83.7%; RP: 83.1%) were treated with a single infusion of FRT; 18.3% and 12.3% of bleeds in the OD and RP group, respectively, were treated with 2 infusions; in the RP group, 2.9% of bleeds were treated with 3 infusions and 1.7% of bleeds were treated with ≥4 infusions (5/6 were spontaneous joint bleeds). For both OD and RP pts with HA or HB, the most frequently used FRT to treat acute breakthrough bleeds was pd or SHL product; 401/453 (88.5%) bleeds were treated with po or SHL product (HA: 351/375 [93.6%]; HB: 50/78 [64.1%] bleeds). For OD pts with HA during ATP, the mean (SD) pd/SHL FVIII dose/infusion was 24.19 (7.98) IU/kg (n=19) (OP: 21.63 [10.72] IU/kg [n=26]) and mean (SD) EHL FVIII dose/infusion was 19.93 (5.67) IU/kg (n=4) (OP: 16.46 [5.05] IU/kg [n=8]). For RP pts with HA during ATP, the mean (SD) pd/SHL FVIII dose/infusion was 24.61 (8.09) IU/kg (n=40) (OP: 28.06 [8.83] IU/kg [n=37]) and mean (SD) EHL FVIII dose/infusion was 30.57 (9.83) IU/kg (n=4) (OP: 43.44 [8.59] |U/kg [n=5]). In all OD and RP pts with HA, 80.4% and 82.4% of acute bleeds were treated with a single infusion of FRT, respectively. For OD pts with HB during ATP, the mean (SD) pd/SHL FIX dose/infusion was 23.70 (7.15) IU/kg (n=3) (OP: 23.76 [10.77] IU/kg [n=5]) and mean (SD) EHL FIX dose/infusion was 12.60 (5.06) IU/kg (n=2) (OP: 13.16 [5.65] IU/kg [n=4]). For RP pts with HB during ATP, the mean (SD) pd/SHL FIX dose/infusion was 49.51 (26.40) IU/kg (n=5) (OP: 47.28 [17.10] IU/kg [n=6]) and mean (SD) EHL FIX dose/infusion was 47.04 (11.53) IU/kg (n=6) (OP: 74.36 [21.47] IU/kg [n=4]). In OD and RP pts with HB, 100.0% and 85.7% of acute bleeds were treated with a single infusion of FRT, respectively. For RP pts with HB, FIX consumption was influenced by 2 marstacimab-treated adolescents with several traumatic bleeds that required FRT. No thromboembolic events were reported in association with concomitant FRT use.

Conclusions: In the BASIS study, for pts with HA or HB without inhibitors, acute breakthrough bleeding episodes were successfully managed with episodic FRT during concurrent QW marstacimab prophylaxis and marstacimab was generally safe. Most acute breakthrough bleeds were managed with a single infusion of FRT, and the most common treatment agents were SHL FVIII products (recombinant or pd).

Outcomes of marstacimab treatment in adolescent participants with Hemophilia A or B without inhibitors compared with prior routine prophylaxis: Results from the phase 3 BASIS trial (Abstract 4845, ASH 2025)

A. Chan et al

Background: BASIS (NCT03938792) is an open-label, phase 3 trial of anti-tissue factor pathway inhibitor (TFPI) antibody marstacimab in adult and adolescent participants (pts) with severe hemophilia A (HA; factor VIII <1%) or moderately severe to severe hemophilia B (HB; factor IX ≤2%) with or without inhibitors. Across all pts without inhibitors, marstacimab significantly reduced the annualized bleeding rate (ABR) of treated bleeds compared with prior on-demand (OD) or routine prophylaxis (RP) factor replacement therapy. We report outcomes in adolescent pts without inhibitors who received prior RP.

Methods: Screened male adolescents without inhibitors completed a 6-month observational phase (OP) on RP or OD therapy before receiving a single subcutaneous (SC) loading dose of 300 mg marstacimab followed by 150 mg once weekly (QW) in the 12-month active-treatment phase (ATP). After Day 180, pts meeting prespecified dose escalation criteria (weight ≥50 kg, ≥2 spontaneous bleeds requiring treatment in 6 months) could increase their dose to 300 mg QW. Efficacy assessments included ABRs of treated bleeds and specific bleed types. Safety (including incidence and severity of adverse events [AEs] and immunogenicity) and pharmacokinetic (PK)/pharmacodynamic (PD) parameters were also assessed.

Results: As of April 2023, 18 adolescent pts aged ≥12 to <18 years with HA (n=13) or HB (n=5) without inhibitors entered the OP and received RP before entering the ATP (data from OD pts [n=2] not reported). One pt (administered 1 dose of marstacimab in the ATP) was later excluded from analyses due to termination of study site. Most pts were from Europe (50.0%), predominately Turkey (38.9%). At baseline, 5 pts (27.8%) had ≥1 target joint. A numerical reduction in mean ABR of treated bleeds was observed with marstacimab in the ATP vs RP in the OP (2.98 vs 3.36, n=17; compared with 5.74 vs 9.11 in adults, n=66). Mean (median) ABR during the ATP was 1.63 (0.00) for joint bleeds, 0.75 (0.00) for spontaneous bleeds, 0.00 (0.00) for target joint bleeds, and 3.39 (0.00) for total (treated and untreated) bleeds. The median ABR of treated bleeds in the ATP was 0.00, with significant variability in pts with HB (n=4). Two pts with HB had 0 treated bleeds; 2 pts had ABRs of 19.48 and 11.10 (majority traumatic bleeds). Mean (SD) annualized total factor consumption unrelated to bleeding events also decreased in the ATP vs the OP: 20 (80) vs 3308 (1063) IU/kg, n=17. In all, 36 AEs were reported in 14/17 pts (82.4%) during the ATP vs 11 AEs in 7/18 pts (38.9%) in the OP. Treatment-related AEs were reported in 4 pts, all related to injection site (erythema, edema, and swelling [n=1 each]; pruritus [n=2]). One serious AE of tympanic membrane perforation was reported in 1 pt in the ATP who temporarily discontinued treatment 10 days prior to tympanoplasty/ear tube insertion. Preventative factor replacement therapy was given peri and post operatively, and the pt resumed treatment 6 days post procedure. One other pt temporarily discontinued treatment due to an AE of COVID-19. No deaths, study discontinuations, or thromboembolic events were recorded. Two pts had their dose increased to 300 mg QW; neither reported any AEs post dose escalation. Antidrug antibodies developed in 2/17 pts, 1 of whom was also positive for neutralizing antibodies, transient in nature. Marstacimab plasma levels were ~ 2 to 2.5-fold higher in adolescents vs adults. For pts receiving 150 mg QW marstacimab, median steady-state plasma concentrations were ~25,000-30,000 ng/mL in adolescents vs ~10,000-11,000 ng/mL in adults. Population PK analysis found marstacimab clearance (CL) was 29% lower in adolescents vs adults; weight-adjusted CL was 3% lower in adolescents, indicating weight accounted for most of the CL differences. In general, no clinically relevant differences were seen in steady-state median ranges of PD endpoints following 150 mg QW marstacimab in adolescents (n=17) vs adults (n=85): peak thrombin, 41-54 vs 63-66 nM; prothrombin fragment 1+2, 557-874 vs 492-579 pmoL/L; D-dimer, 0.3-0.4 vs 0.3 ug/mL; total TFPI, 389-495 vs 268-283 ng/mL.

Conclusion: Compared with previous RP therapy, SC QW marstacimab reduced bleeding in adolescent pts with HA or HB without inhibitors and was generally well tolerated. No clinically relevant differences in PD endpoints were observed compared with adults and PK differences were explained by weight.

Long term effect of marstacimab prophylaxis in hemophilia A and B on target joints: Results from BASIS and OLE studies (Abstract 4844, ASH 2025)

V. Jiménez-Yuste et al

Background: Marstacimab is a tissue factor pathway inhibitor (TFPI) antagonist recently approved for prophylactic treatment of hemophilia A (HA) and hemophilia B (HB) in people without inhibitors. In the phase 3 BASIS trial (NCT03938792) and its open-label extension (OLE) study, marstacimab was well tolerated, with high efficacy in bleed prevention. The majority of participants in the BASIS trial presented with a severe bleeding phenotype with a high number of target joints (TJs) at the time of study entry. We report on the impact of marstacimab on TJ outcomes.

Methods: BASIS enrolled males aged ≥12 to <75 years with severe HA (factor VIII [FVIII] < 1%) or moderately severe to severe HB (factor IX [FIX] ≤2%) who were receiving on-demand (OD) or routine prophylaxis (RP) treatment. Following a 6-month observational phase (OP), participants entered a 12-month active treatment phase (ATP) and received a single loading dose of marstacimab 300 mg subcutaneous (SC), followed by marstacimab 150 mg SC once weekly (dose escalation to 300 mg was allowed after Day 180 per investigator's discretion), which was continued in the OLE. TJs were defined by the International Society on Thrombosis and Hemostasis as in those experiencing ≥3 spontaneous bleeds within a consecutive 6-month period. A TJ was considered resolved if it had ≤2 bleeds in a consecutive 12-month period.

Results: 116 participants without inhibitors (n=33 OD, n=83 RP) entered the BASIS ATP. Of these, 107 (n=32 OD, n=75 RP) completed an additional 12 months in the OLE as of the April 2024 data cutoff. In total at ATP baseline, 80/116 participants (n=33 OD, n=47 RP) had ≥1 TJ and 25 had ≥3 TJs; 58/80 (72.5%) of participants with 21 TJ were <45 years old. There were 181 TJs (79 OD; 102 RP); the most frequent locations were knees (65), ankles (52), and elbows (48). Among OD participants with 1, 2, and ≥3 TJ, respectively, at baseline, the mean (SD) [median (Q1, Q3)] ABR of treated bleeds (any location) during OP was 26.15 (16.42) [23.19 (18.47, 36.31)], 42.32 (22.23 [40.37 (20.29, 57.17)], and 44.41 (23.52) [41.95 (24.65, 65.10)], and decreased during ATP to 1.01 (1.53) [0.00 (0.00, 2.03)], 3.88 (3.56) [2.03 (1.50, 6.10)], and 3.71 (5.0) [2.02 (0.00, 5.54)]. Among RP participants with 0, 1, 2, and ≥3 TJ, respectively, at baseline, mean (SD) [median (Q1, Q3)] ABR of treated bleeds (any location) during OP was 4.44 (6.75) [1.94 (0.00, 6.77)1, 10.73 (16.44) [3.84 (0.00, 12.59)], 9.68 (13.74) [3.95 (0.00, 18.06)], and 11.49 (17.80) [4.35 (0.00, 11.78)] and during ATP was 2.69 (4.36) [1.01 (0.00, 3.05)], 4.68 (7.85) [1.01 (0.00, 5.09)], 7.39 (10.11) [5.04 (0.00, 7.10)], and 10.24 (11.06) [4.73 (2.32, 13.78)]. A total of 155/181 (85.6%; 73 OD, 82 RP) TJs resolved in the ATP. The mean (SD) [median (Q1, Q3)] ABR of treated TJ bleeds from baseline to ATP and OLE, respectively, was consistently and progressively reduced; OD: 23.20 (20.52) [15.63 (5.83, 35.28)], 1.82 (2.90) [1.01 (0.00, 2.02)1, 1.16 (1.94) [0.51 (0.00, 1.65)], and RP: 3.38 (8.32) [0.00 (0.00, 1.97)], 2.29 (5.52) [0.00 (0.00, 1.38)], 1.40 (5.03) [0.00 (0.00, 0.69)]. The mean (SD) [median (Q1, Q3)] ABR of treated TJ bleeds from baseline to ATP and OLE, respectively, also progressively decreased when analyzed by hemophilia type: 10.09 (16.90) [0.00 (0.00, 12.41)], 2.37 (5.42) [0.00 (0.00, 2.00)] and 1.50 (4.84) [0.00 (0.00, 1.24)] for HA and 5.12 (9.67)

[0.00 (0.00, 5.83)], 1.36 (2.15) [0.00 (0.00, 3.04)], and 0.73 (1.57) [0.00 (0.00, 0.75)] for HB. Resolution of ≥1 TJ occurred in 73/80 (91.3%) participants (n=32/33 OD, n=41/47 RP) during the ATP and in 68/72 (94.4%) participants (n=31/32 OD, n=37/75 RP) in the OLE. In the ATP and OLE, resolution of all TJs occurred in 23/26 (88.5%) and 19/22 (86.4%) participants with 1 TJ at baseline, 20/29 (69.0%) and 22/26 (84.6%) participants with 2 TJs, and 19/25 (76.0%) and 21/24 (87.5%) participants with ≥3 TJs.

Conclusion: Marstacimab prophylaxis was generally safe and led to sustained and clinically meaningful reductions in TJ bleeding and high rates of joint resolution, even among patients with severe baseline joint involvement. These findings reinforce the long-term efficacy of marstacimab in people with severe HA or HB without inhibitors.

Characterization of participants with elevated bleeding rates responding to prophylactic marstacimab treatment in the phase 3 BASIS trial (Abstract 4838, ASH 2025)

Y. S. Park et al

Background: Marstacimab, a monoclonal antibody targeting tissue factor pathway inhibitor to reduce inhibition of the extrinsic coagulation pathway and rebalance hemostasis, is approved for prophylaxis in patients with hemophilia A (HA) or B (HB) without inhibitors. The phase 3 BASIS study (NCT03938792) demonstrated marstacimab was effective in reducing treated annualized bleeding rate (ABR) vs prior on-demand (OD) or routine prophylaxis (RP) therapy in participants (pts) with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%) without inhibitors. Marstacimab was generally well tolerated with no unanticipated side effects. However, some pts had high ABRs during marstacimab treatment that deviated from the overall study population. Understanding factors that influence responder outcomes is crucial for personalized treatment and effective management of hemophilia. We aimed to identify prognostic factors for pts with elevated ABRs in BASIS.

Methods: Eligible pts were male, aged ≥12 to <75 years with severe HA or moderately severe to severe HB with or without inhibitors. Results are reported for the noninhibitor cohort. Pts entered a 6-month observational phase (OP) and received prescribed factor replacement therapy (OD or RP) before receiving a single subcutaneous (SC) dose of 300 mg marstacimab (2×150 mg) followed by 150 mg SC once weekly (QW) in the 12-month active treatment phase (ATP). Dose escalation to 300 mg was allowed per investigator's discretion after Day 180 for pts who met protocol-specified criteria based on breakthrough bleeding. After completing the ATP, pts could enroll in the open-label extension (OLE) study (NCT05145127). Pts with elevated ABRs were identified based on the data distribution of ABR in the ATP from all pts (OD+RP); pts with an ABR in the ATP greater than the mean ABR+1.5x interquartile range (ie, ABR >12) were assessed. Prognostic factors evaluated for an elevated ABR were age, region, hemophilic arthropathy, baseline hemophilia joint health score (HJHS) total score and number of target joints at baseline. Descriptive data are presented.

Results: In all, 116 pts received marstacimab in the ATP. Model-based mean ABR (95% CI) decreased from the OP to the ATP in OD and RP groups (OD: 39.9 [33.1-48.1] vs 3.2 [2.1-4.9]; RP: 7.9 [5. 1-10.7] vs 5.1 [3.4-6.8]). Overall, 12 pts (OD: n=1; RP: n=11; HA: n=10; HB: n=2) with an ABR >12 in the ATP were identified. At baseline, most (n=11; 92%) pts were aged >18 y (5 [42%] ≥45 y), 6 (50%) pts were Asian and 6 (50%) were White. Most (n=11; 92%) had ≥1 target joint (≥3 target joints: n=5, 42%) and 8 (67%) had hemophilic arthropathy.

Compared with the lower ABR group (ABR ≤12), the group with elevated ABRS (ABR >12) was comprised of a higher percentage of adults (OD: 100% vs 93.8%; RP: 90.9% vs 77.8%), a higher percentage with hemophilic arthropathy (OD: 100% vs 50%; RP: 63.6% vs 54.2%), a higher mean HJHS total score indicative of worse joint health (OD: 29.0 vs 21.0; RP: 22.7 vs 16.8), more target joints at baseline (pts with ≥3 target joints: OD: 100.0 vs 34.4; RP: 36.4 vs 12.5) and a greater proportion of RP pts from Asia (OD: 0% vs 65.6%; RP: 54.5% vs 33.3%). Although these pts had a higher ABR during the ATP (range 13.8-35.5) vs the lower ABR group (range 0.0-11.2), 41.7% (n=5/12) had a mean decrease in ABR of 55.4% (SD 28.1) vs the OP. Of the pts with an elevated ABR, 5 (42%) dose-escalated to marstacimab 300 mg SC QW; ABR decreased in all pts after dose escalation (range 0.0-10.1). Neutralizing antibodies were detected in 1 pt at Day 60; titers were transient and resolved by Day 180. Eight (67%) pts with an elevated ABR continued into the OLE (3 discontinued early, 1 chose not to enroll) and continued ABR improvements were observed in 7 (88%) pts.

Conclusions: Twelve pts had an ABR >12 during the ATP. The sample size precludes definitive conclusions on prognostic factors but variables associated with an elevated ABR included older age, residence in Asia, hemophilic arthropathy, higher baseline HJHS total score and baseline target joints. Worse joint disease correlated with a higher ABR. However, most pts with an elevated ABR showed ABR reductions during the ATP or OLE, suggesting these pts still responded to marstacimab. Dose escalation to marstacimab 300 mg SC QW led to reduced ABR in all pts with an elevated ABR who escalated, suggesting this may be an option for select pts.

Evaluation of the combined effects of emicizumab and marstacimab in plasma from Hemophilia A patients using thrombin generation assay (Abstract 4834, ASH 2025)

M. Ronconi et al

Background: Patients with Hemophilia A (HA) may be treated with prophylactic emicizumab therapy, a bispecific monoclonal antibody that promotes coagulation by bridging factor IX (FIX) and factor X (FX). Marstacimab has been recently approved for the prevention of bleeding events in patients with hemophilia A and B. Marstacimab is a human monoclonal antibody targeting the K2 domain of TFPI to improve thrombin generation and restore hemostasis. As both agents are non-replacement therapies with distinct mechanisms of action and half-life, transitioning between them raises questions about the potential risk of excess thrombin generation (TG) and safety.

Objective: To test the potential additive effect of marstacimab on thrombin generationex vivo using plasma collected from a cohort of eight severe hemophilia A (HA) patients receiving emicizumab as part of their standard prophylactic treatment regimen.

Methods: Platelet poor plasma was obtained from adult male patients (age 20-54) with severe HA on stable prophylaxis with emicizumab for at least 6 months and did not receive any additional hemostatic therapy in the previous 4 weeks. Samples were spiked with various concentrations of marstacimab (4, 16, 80 ug/mL). Additionally, to mimic the effect of addition of FVIII products as in the case of the treatment of a breakthrough bleed, we spiked the plasma with FVIII (0.4 IU/mL). Tissue factor (Recombiplastin 2G, HemosIL) was used as trigger, and the assay was allowed to run for 90 minutes, with fluorescence readings occurring at 1-minute intervals throughout. TG was performed using a SpectraMax M5 plate reader with SoftMax Pro v.7 software (Molecular Devices). TG parameters (peak thrombin, lag time, and endogenous thrombin potential [ETP]) were determined analyzing data using the Technothrombin TGA Evaluation Software (Technoclone). Commercial

normal pooled plasma (NPP) and FVIII depleted plasma (F8DP), plasma from healthy donors (CTRL), and HA plasma with residual <1% FVIII activity spiked with 0.2 IU/mL and 0.8 IU/mL were used as controls.

Results: In plasma from healthy donors, ETP, peak thrombin and lag time values ranged from 2,552 to 2,872 nM*min, 124 to 223 nM, and 11-13 minutes respectively. There was no significant thrombin generation detected in severe HA plasma used as a control. When F8DP was supplemented with 0.8 IU/mL mean (range) values for ETP, peak thrombin and lag time were 3,059 nM*min (2603-3302 nM*min), 157.4 nM (122.6-212.5 nM), and 13.2 minutes (12-14 minutes), respectively.

At baseline, plasma from patients receiving emicizumab showed a mean ETP of 3,177.3 (range: 2212-3778 nM*min), mean peak thrombin of 94 nM (range: 49.8-109.4 nM) and mean lag time of 13.3 minutes (range: 12-15.5 minutes). Addition of marstacimab to plasmas of patients on treatment with emicizumab resulted in a significant improvement in all the parameters tested. When spiked with 16 ug/mL of marstacimab (expected average steady state marstacimab concentration in patients), mean ETP and peak thrombin were higher than baseline and closer to the range of values obtained in healthy controls and NPP. The lag time was shortened and similar to controls and NPP. At the highest concentration tested (marstacimab 80 ug/mL) mean ETP was 3,503.4 nM*min (range: 3212-3987 nM*min), mean peak thrombin was 189.8 nM (range: 175.2-208.2 nM) and mean lag time was reduced to 9 minutes (range: 8-11 minutes).

Additionally, patient plasma samples spiked with both marstacimab 80 ug/mL and FVIII 0.4 IU/mL showed no significant changes in the mean ETP, (3,460 nM*min, range: 2688-3902 nM*min), a modest increase in mean peak thrombin (202.4 nM; range:181.2-241 nM), and similar mean lag time (9.9 minutes; range: 9-12 minutes) compared to the spike with Marstacimab 80 ug/mL only.

Conclusion: Our data show that addition of marstacimab to plasma from patients on prophylaxis with emicizumab resulted in a dose-dependent increase in peak thrombin generation and ETP, while also reducing lag time. These changes consistently remained mostly within the range observed in healthy donors. Overall, no evidence of excessive thrombin generation was detected, even at the highest concentrations of marstacimab tested. While the clinical safety of switching between emicizumab and marstacimab remains to be established in future clinical studies, these findings provide supportive evidence for absence of excessive thrombin generation.

Von Willebrand Disease and Other Rare Bleeding Disorders

Emicizumab for severe von Willebrand disease (VWD): the EmiVWD study interim analysis (IIS) (Abstract 1315, ASH 2025)

J. Roberts et al

Background and Significance: Von Willebrand Disease (VWD) is the most common inherited bleeding disorder affecting up to 0.1-1% of the population, typically characterized by mucocutaneous bleeding. There is increased focus on prophylaxis for VWD with severe bleeding phenotypes, currently limited treatment options, and non-intravenous therapeutics are desired to tailor therapy for patient needs. Emicizumab is a monoclonal, bispecific antibody that demonstrates factor VIII-like activity enhancing thrombin generation, transforming prophylactic therapy for many with hemophilia A. Emicizumab can be administered subcutaneously at a frequency less than that of other currently available therapies for VWD, with a half-life of 27 days. Based on available literature emicizumab has been utilized successfully for VWD prophylaxis, and further investigation is warranted. Our objective is to evaluate the safety and efficacy of emicizumab for prophylaxis in severe VWD compared to the preceding 12-month bleed history.

Study Design and Methods: We initiated a pilot multicenter, prospective open-label study (NCT05500807) to evaluate emicizumab prophylaxis in severe VWD type 3, or VWD with VWF antigen (VWF:Ag), VWF activity (VWF:RCo or VWF:GPIbM), or VWF collagen binding (VWF:CB) ≤20 IU/dl or variant VWD confirmed by genetic mutation or additional VWF activity assays (ie. VWF platelet binding, VWF:FVIII binding, VWF propeptide), or VWD with concomitant hemophilia A defined as VWF:Ag, VWF activity, or VWF:CB < 50 U/dl, and mild, moderate or severe hemophilia A based upon historical medical records, with indication for hemostatic prophylaxis. Targeted enrollment is 40 patients of any age (≥3 kg). Exclusion criteria include patients with non-severe VWD, other bleeding disorders, renal and/or hepatic impairment, emicizumab treatment in the previous 18 months, or previous treatment thromboembolic disease in the past 12 months. Pre-investigation annualized bleed rate and hemostatic therapies are determined by a one-year retrospective chart review, collected at the time of enrollment. Patients then receive Emicizumab, 3mg/kg weekly for 4 consecutive weeks, followed by once weekly dosing of 1.5mg/kg for 52 weeks total therapy. Dose up-titration to 3 mg/kg once weekly will be allowed if suboptimal efficacy. Treatment records are maintained along with bleeding event logs. Patients are closely monitored for safety and tolerability. Breakthrough bleeding events may be treated with the patients usual on-demand products per the investigator's discretion. Central clinical laboratory testing will be completed, in addition to genetic testing. Patient-reported outcomes (PROMIS-29 PROs, SF-36) will be gathered to gain understanding on the impact of treatment on patients. Analysis will be performed through descriptive statistics to determine proof of principle, with patient bleeding evaluated prior to and after emicizumab prophylaxis. End of study is expected to occur 18 months after the last patient's first dose of study drug, to include a 6-month post-emicizumab prophylaxis follow-up. The primary hypothesis is that emicizumab is safe and efficacious for prophylaxis in VWD. Secondary objectives include evaluation of treatment burden vs VWF concentrate prophylaxis, bleed rate and severity, VWF qualitative defects or genetic mutations that may have impact on

emicizumab clinical response. Exploratory objectives include evaluation of health-related quality of life, impact on VWF concentrate use with bleeding events, surgeries, and heavy menstrual bleeding. Total length of the study is expected to be approximately 36 months. Six centers in the United States have currently been enrolling patients. Enrollment is currently ongoing.

Conclusions: This ongoing pilot study is the first prospective investigation of emicizumab in patients with severe VWD. This study will shed light on feasibility, safety and potential efficacy of emicizumab prophylaxis in this patient population.

Subcutaneous, every-four-week maintenance dosing of a novel protein S antibody is well tolerated and substantially reduces bleeding rates: Results from A phase 1/2 multidose study of VGA039 in patients with von Willebrand disease (Abstract 308, ASH 2025)

A. Wheeler et al

Introduction: Patients with von Willebrand Disease (VWD) experience frequent, prolonged bleeding of variable types and severity. Recurrent and severe bleeds are often treated with therapies that are associated with side effects or require frequent intravenous infusions of factor concentrate, resulting in suboptimal bleed protection and high treatment burden. VGA039 is a fully human, |gG4 monoclonal antibody that inhibits the cofactor activity of Protein S to enhance both primary and secondary hemostasis by promoting thrombin generation. In a single-ascending-dose study, VGA039 showed marked reductions in bleeding rates associated with VGA039 concentrations ≥25 ug/mL. The aim of this study was to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of multiple administrations of subcutaneous (SC) VGA039 in patients with VWD.

Materials and Methods: This open-label, phase 1/2 study (NCT05776069; VIVID-3) was conducted in adolescents and adults with VWD. Key eligibility criteria included: (1) symptomatic VWD of any type or subtype, (2) baseline FVIII activity at or below the lower limit of normal, (3) and no laboratory evidence of thrombophilia or prior history of thromboembolism. Dosage regimens for each cohort were determined in conjunction with an independent Data Monitoring Committee. Patients received scheduled doses of SC VGA039 over 120 days, followed by a follow-up period up to 42 days during which patients had the option to transition to an open-label extension study. Safety, pharmacokinetic, and pharmacodynamic parameters were collected at regular intervals, and participants recorded information on bleeding and treatments in a weekly diary.

Results: As of July 31, 2025, 11 patients aged 15-53 years with various VWD types/subtypes, including types 1, 2A, 2M, or 3, participated in the study and received a treatment regimen consisting of a single SC loading dose on Day 1, followed by 5 SC maintenance doses starting on Day 8 and continuing every 4 weeks (Q4W) thereafter through Day 120. Six patients in Cohort MD-1 received a flat dose level of 225 mg SC VGA039. Five patients in Cohort MD-2 received weight-banded dose regimen of 187.5 mg (45-<60 kg), 262.5 mg (60-100 kg), or 450 mg (≥100 kg) SC VGA039. As of July 31, 2025, there have been no drug-related AEs except for 2 events of headache in 1 patient, no thromboembolic events, and no injection site reactions reported. No clinically significant elevations in D-dimer levels were observed. One patient has completed the study as of July 31, 2025. This patient was on VWF-containing concentrate prophylaxis and still had a pre-study historical annualized bleeding rate of 56.8. Prior to study start, prophylaxis was discontinued and washed out. VGA039 concentrations were maintained within target concentrations and associated with a

substantial (74%) reduction in bleeding over 148 days compared to prior prophylaxis, with unremarkable D-dimer levels throughout the study. During the follow-up period, the subject elected to directly transition into the open-label extension study to continue VGA039 treatment. Beyond this first patient, preliminary efficacy and safety data in other patients in this cohort show similar reductions in bleeding without meaningful changes in D-dimer levels. Updated safety, bleeding rates, and pharmacokinetics for all patients in both cohorts will be presented at the meeting.

Conclusions: VGA039 was safe and well tolerated over multiple doses in Type 1, 2, and 3 VWD subjects weighing 45-160.5 kg. Preliminary findings suggest substantial reductions in bleeding rates following a single SC loading dose and every-four-week maintenance dosing schedule in patients reporting high historical bleed rates prior to entering the study. These data inform selection of a dosage regimen optimized for durable bleed control with a favorable safety profile for assessment in a Phase 3 trial of VGA039 as every-4-week subcutaneous prophylaxis for patients with VWD of all types.

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	Bispecific antibody binding to FVIIa and TLT-1	Subcutaneous	Hemab	Phase 1/2
Aptamer	Haemophilia A, Type 2B VWD	Rondoroptivon pegol BT200	Pegylated aptamer binding to vWF	Subcutaneous	Medical University of Vienna	Phase 2

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

GENE THERAPY 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	Single intravenous infusion	Spark	Refocus on developing an enhanced-function

			liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette			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	Pre-clinical phase
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	Fdanacogene elaparvovec (formerly SPK-9001)	Padua variant (rAAV-Spark100) (fidanacogene elaparvovec)	Single intravenous infusion	Pfizer (Originally Spark)	Discontinued
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 in Europe, U.S., UK and Canada (brand name Hemgenix)
Gene Therapy	Haemophilia B	AMT-060	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	Pre-clinical phase
Gene Therapy	Haemophilia B	BBM-H901	Engineered liver-tropic AAV vector expressing a hyperactive Padua FIX	Single intravenous infusion	Belief BioMed	Phase 3
Gene Therapy	Haemophilia B	-	CRISPR/Cas9-based Factor 9 (*F9*) gene-insertion therapy	Single intravenous infusion	Regeneron	Planned launch of Phase 1 clinical trial in 2024
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 Engineering Sciences (TTW), 'Connecting Innovators' Open Technology Programme, Project#18712	Pre-clinical phase

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	Launch of Phase 1/2 trial (BeCoMe-9) in late 2024

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	Approved by EMA in July 2024

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-	Octapharma	Licensed

			human FVIII (simoctocog alfa human-cl-rhFVIII)		
Replacement FVIII	Haemophilia A	Refacto AF®	Moroctocog alfa	Pfizer	Licensed
Replacement FVIII plasma-derived	Haemophilia A	Octanate	-	Octapharma	Licensed
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	-	Kedrion	Licensed

		but they are not the only ones: there are also Proplex, Kedcom, Protromplex			
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	Licenced

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	Conditional licensing in Europe, available only in the US, Germany and Italy
Gene Therapy	Haemophilia B	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	CSL Behring	Licensed in the UK, the US and in Europe
Gene Therapy	Haemophilia B	BEQVEZ® PF-06838435 fidanacogene elaparvovec (formerly SPK-9001)	Padua variant (rAAV-Spark100) (fidanacogene elaparvovec)	Pfizer	Commersalisation stopped

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