EHC
Empowering the bleeding disorders community

Novel Treatment Review (NTR)

A periodic EHC Review

July 2025 - Issue

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Foreword

Welcome to the second edition for 2025 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 European Association for Haemophilia and Allied Disorders (EAHAD) Congress held in February 2025, WFH Comprehensive Care Summit held in April 2025 and the International Society on Thrombosis and Haemostasis (ISTH) Congress held in June 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 January 1, 2025.

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

EAHAD abstracts: https://onlinelibrary.wiley.com/toc/13652516/2025/31/S1
WFH abstracts: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.70032
ISTH abstracts: https://www.rpthjournal.org/issue/S2475-0379(25)X0006-6

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
- Mr David Page, Canadian Haemophilia Society
- Dr Uwe Schlenkrich, EHC volunteer
- Miguel Crato, EHC President

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 prothrombin complex*	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 concetrates*	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 / pharmacodynamics*
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*

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

Factor Replacement Therapies

The National Institute for Health and Care Excellence (NICE) has issued final guidance recommending Efanesoctocog alfa—marketed as Altuvoct in Europe and Altuviiio in the U.S.—as a treatment option for people aged 2 and older with severe hemophilia A in England and Wales. This follows its approval by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) earlier this year.

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

The antibody therapy Mim8 (denecimig) was well tolerated and effectively controlled bleeding in children with hemophilia A, regardless of inhibitor status. These results come from interim data from the now-completed Phase 3 FRONTIER3 study (NCT05306418), which enrolled children aged 1–11. The findings align with recent results from the Phase 3 FRONTIER2 trial (NCT05053139), where Mim8 significantly reduced bleeding in adults and adolescents with hemophilia A.

Rebalancing therapies

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has approved Pfizer's marstacimab, marketed as Hympavzi, for the prevention and reduction of bleeding in patients aged 12 and older with severe hemophilia A or B who have not developed inhibitors to factor VIII or IX.

The U.S. Food and Drug Administration (FDA) has approved fitusiran, marketed as Qfitlia, as a routine prophylactic treatment to prevent or reduce bleeding episodes in people aged 12 and older with hemophilia A or B, with or without inhibitors or antibodies that can reduce the effectiveness of treatment.

Gene therapy for haemophilia A

Metagenomi is conducting preclinical studies to advance MGX-001, its experimental gene-editing therapy for hemophilia A, with the goal of entering clinical trials in 2026.

An experimental gene therapy using modified blood stem cells enabled five adults with severe hemophilia A to achieve therapeutic levels of clotting factor VIII (FVIII), effectively preventing and controlling bleeding, according to a small first-in-human study. During the Phase 1 trial (NCT05265767), none of the five participants experienced bleeding episodes after receiving autologous stem cells engineered with a lentiviral vector carrying the genetic instructions to produce functional FVIII.

Mary Eapen et al reported results from a gene therapy trial for severe hemophilia A in patients with a history of factor VIII inhibitors. In the first participant, 24-month follow-up confirmed the feasibility and safety of the approach, providing preliminary evidence in humans that the ITGA2B gene promoter can effectively drive platelet-derived factor VIII expression.

Gene therapy for haemophilia B

Pfizer is discontinuing the global development and commercialization of Beqvez, its gene therapy for hemophilia B. The company will instead focus on advancing Hympavzi, an anti–tissue factor pathway inhibitor for both hemophilia A and B.

Participant recruitment is now open for the BEYOND9 and BECOME9 studies.

Monovalent Antibody

At ISTH 2025, investigators presented data from the first-in-human Phase 1/2 clinical trial, "Velora Pioneer" (NCT06754852), evaluating HMB-002 in patients with Von Willebrand Disease (VWD). Hemab Therapeutics also shared preclinical findings supporting the development of HMB-002. Initial cohort results demonstrated a favorable safety profile. Pharmacodynamic analyses showed encouraging accumulation of endogenous VWF and Factor VIII, with mean VWF levels increasing more than 1.5-fold above baseline within 14 days of a single 20 mg subcutaneous dose. These increases in Factor VIII were associated with temporary normalization of activated partial thromboplastin time (APTT) and enhanced thrombin generation, suggesting a restoration of hemostatic balance.

Section 2 - Report highlights

An update on novel therapies in haemophilia A

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

NXT007

A bispecific antibody NXT007 exerts a hemostatic activity in hemophilia A monkeys enough to keep a nonhemophilic state

Yuri Teranishi-Ikawa et al. reported that NXT007 exhibited in vitro thrombin generation activity comparable to the international standard activity of FVIII (100 IU/dL), significantly higher than that of emicizumab when triggered by tissue factor. Additionally, NXT007 demonstrated potent in vivo hemostatic activity at approximately 30-fold lower plasma concentrations than those historically observed with emicizumab. The dose-response relationship between NXT007 and emicizumab was consistent across both in vitro and in vivo studies. Regarding pharmacokinetics, NXT007 showed lower in vivo clearance compared to typical monoclonal antibodies, indicating that Fc engineering to enhance FcRn binding was effective.

NXT007 Prophylaxis in Emicizumab-Naive Persons with Hemophilia A without Inhibitor: Phase I/II Study

Midori Shima et al. presented Phase I/II study results suggesting that NXT007 has the potential to achieve coagulation activity within the non-hemophilic range in people with hemophilia A (PwHA), with a tolerable safety profile—supporting progression to the next phase of clinical studies.

Factor Replacement Therapies

Efanesoctocog alfa (brand name **Altuvoct)**

Treatment of Bleeding Episodes with Efanesoctocog Alfa in Children: XTEND-ed Second Interim Analysis

Lynn Malec presented the second interim analysis from the XTEND-ed study evaluating efanesoctocog alfa for treating bleeding episodes in children with haemophilia A. The data demonstrated sustained haemostatic efficacy, rapid bleed control, and no unexpected safety concerns. Importantly, the treatment maintained consistent performance during extended use in the paediatric cohort, reinforcing its potential as a reliable, long-acting FVIII replacement for routine care.

An update on novel therapies in haemophilia B

Gene Therapy

Etranacogene dezaparvovec

Etranacogene dezaparvovec in haemophilia B: a 48-month post hoc responder analysis of HOPE-B

In an oral presentation at ISTH 2025, it was reported that a single dose of etranacogene dezaparvovec provides durable FIX-Padua expression, sustained reduction in annualised bleeding rate (ABR), and a significant decrease in FIX consumption over four years. Etranacogene dezaparvovec remained well tolerated, with two new cancers reported that were unrelated to the AAV vector.

ETX-148

Efficacy and Safety of ETX-148 in Murine Models of Haemophilia A and B

In an oral presentation at EAHAD 2025, N. Pursell et al. presented preclinical data on ETX-148. The results highlight ETX-148's potential as a safe and effective prophylactic treatment for haemophilia, featuring a patient-friendly quarterly subcutaneous dosing regimen.

An Update on Rebalancing Therapies

Concizumab

Annualized bleeding rates in hemophilia A/B and target joints: Concizumab explorer8 study

In an oral presentation at ISTH 2025, A. Wheeler et al. presented the Explorer8 study, which evaluated once-daily subcutaneous concizumab in patients with haemophilia A or B (with or without inhibitors) who had target joint issues. The presentation revealed that over a 56-week period, concizumab reduced median annualised bleeding rates and provided significant control of bleeding in target joints. These findings reinforce its efficacy and sustained bleed protection in both types of haemophilia, highlighting its potential as a reliable rebalancing therapy for challenging joint bleeds.

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

HMB-001

Sutacimig (HMB-001), a bispecific antibody developed by Hemab Therapeutics for Glanzmann thrombasthenia (GT), has demonstrated promising safety and efficacy in its Phase 2 study (NCT06211634). In an oral presentation at ISTH 2025, researchers reported that the fully enrolled trial (N=34) showed clinically meaningful reductions in bleeding events, with a greater than 50% decrease in median Annualized Treated Bleeding Rate (ATBR), from 21.2 to 4.61. Select patient reports also indicated reduced bleed severity and decreased use of intravenous rFVIIa.

VGA039

Phase I Study of VGA039, a Protein S-Targeting Monoclonal Antibody, in Individuals With von Willebrand Disease Demonstrates Sustained Drug Concentrations, Increased Thrombin Generation and Decreased Bleeding Following a Single Subcutaneous Injection

In a presentation at EAHAD 2025, A. Chiavarella et al. reported that VGA039 was safe and well tolerated in the subcutaneous single ascending dose (SC SAD) study involving subjects with all types of VWD. Reductions in annualised bleeding rates (ABR) were observed at VGA039 concentrations associated with increased thrombin generation, with no dose-limiting toxicities (DLTs) reported.

Section 3 - research abstracts and articles

Haemophilia A

Bispecific Monoclonal Antibodies Mimetics (including FVIII Mimetics)

Emicizumab (Hemlibra)

Health-related quality of life (HRQoL), physical activity (PA) and joint health in people with severe haemophilia A (PwSHA) and a bleeding phenotype receiving emicizumab – results from the HemiNorth 2 study (PO081, EAHAD 2025)

J. Astermark et al

Introduction: PwSHA can experience bleeding despite receiving Factor (F)VIII prophylaxis. HemiNorth 2 (MO42245; EudraCT# 2020-003256-32) assessed the effectiveness of emicizumab in a physically active cohort of PwSHA who had ≥1 treated joint/muscle bleed in the 52 weeks of the previous HemiNorth non-interventional study [(NIS); MO42590].

Methods: PwSHA rolling over from NIS observation on FVIII prophylaxis received emicizumab per label for 48 weeks. The primary endpoint was HRQoL via the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) for adolescents and adults. Secondary endpoints included PA [International Physical Activity Questionnaire-Short Form (IPAQ-SF) and an intra-participant comparison of FitBit (activity tracker) data between NIS Week 17-24 and treatment Week 41-48], treatment preference [Emicizumab Preference (EmiPref) survey, model-based annualised bleeding rates (ABRs) and adverse events (AEs).

Results: Overall, 28 PwSHA enrolled, all male [median age: 26.5 (range: 12-52) years; median observation time: 50 weeks). Most (12/18) CATCH domain scores were <25 at baseline and remained stable, indicating low bleed risk perception. Treatment burden improved by a mean (standard deviation; % change) of 17.8 (21.1; 55.7%) for adults and 16.7 (15.5; 33.4%) for adolescents from baseline to Week 49. IPAQ-SF scores for moderate/vigorous activity were stable throughout. Mean daily step counts were similar [7982 (NIS) vs. 8619 (HemiNorth 2)]. EmiPref indicated that 23/25 (92.0%) respondents preferred emicizumab over FVIII prophylaxis. From the NIS to HemiNorth 2, model-based ABRs [95% confidence interval (CI); median observation time] for treated bleeds decreased from 5.9 (3.7-9.4; 27 weeks) to 1.6 (0.8-3.2; 48 weeks); participants with zero treated bleeds increased from 8 (28.6%) to 16 (57.1%). A sensitivity analysis performed to exclude one participant (due to low treatment compliance in the NIS) was consistent. One participant reported three serious AEs (deemed unrelated to emicizumab).

Discussion/Conclusion: Emicizumab reduced treatment burden and was preferred over FVIII prophylaxis. PA levels and daily step counts were consistent throughout. Bleeding rates decreased and the number of participants with zero bleeds increased despite consistently high PA. There were no new safety signals.

Joint Health and Physical Activity in People With Haemophilia A Without Factor VIII Inhibitors Before Switching to Emicizumab Prophylaxis: Beyond ABR Study Interim Analysis (PO0105, EAHAD 2025)

G. Castaman et al

Introduction: Advances in haemophilia A (HA) treatment have led to lower annualised bleed rates (ABRs), shifting focus to non-bleed endpoints, for which data are lacking. Beyond ABR (NCT05181618) will evaluate overall health, physical activity (PA) and joint health (JH) in people with HA (PwHA) switching from Factor (F)VIII prophylaxis to emicizumab. This interim analysis reports baseline JH and PA data.

Methods: This Phase IV, multicentre, open-label study will follow PwHA aged 13-<70 years with moderate/severe HA without FVIII inhibitors for 3 years. Preliminary results of baseline JH (elbows, knees and ankles) were evaluated using Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and the International Prophylaxis Study Group (IPSG) MRI scale by an independent review committee, and Haemophilia Joint Health Scores (HJHS) 2.1. PA data were obtained using the International Physical Activity Questionnaire-Short Form (IPAQ-SF).

Results: Overall, 136 PwHA were recruited from 1 tries. Thirty-six (26.5%) were excluded due to previous joint surgery/procedures or <4 joints evaluable with HEAD-US. Of the remaining 100 PwHA, 27 (27%) had all healthy joints; 61 (61%) had both synovitis and osteochondral damage (OCD) in the same and/or separate joints; 6 (6%) had ≥1 joint with synovitis only; and 6 (6%) had OCD only. Median (range) sum of joints HJHS was 0 (0-10) in PwHA with all healthy joints (n = 27) and 11 (0-66) in PwHA with both synovitis and OCD (n = 59). In all PwHA aged 13-17 (n = 24), 30.2% of evaluable joints without previous surgery/procedures had evidence of synovitis and/or OCD; this increased to 35.4%, 53.2% and 73.2% in PHA aged 18-29 (n = 60), 30-49 (n = 43) and ≥50 (n = 9), respectively. Baseline IPSG MRI and HEAD-US scores showed a very strong correlation (Spearman's p value: 0.85). IPAQ-SF data showed little variation in overall PA participation. PwHA with all healthy joints (n = 22) and those with synovitis and OCD (n = 41) reported a median (range) of 0.72 (0.0-13.4) and 0.00 (0.0-10.1) thousand MET/week, respectively.

Discussion/Conclusion: HA substantially impacts JH in those receiving FVIII prophylaxis. JH deterioration is associated with increased age, yet joint deterioration was already present in some adolescents. PwHA with worse JH still report participation in vigorous PA.

Plasma proteomics and collagen biomarkers in people with hemophilia A receiving emicizumab in STASEY (OC 17.2, ISTH 2025)

A. Kiialainen et al

Background: Recurrent joint bleeds in people with hemophilia A (PwHA) can cause joint damage, which releases proteins involved in processes such as cartilage remodeling (e.g. collagen), inflammation and angiogenesis (e.g. cytokines, growth factors) into the blood. Emicizumab, a bispecific monoclonal antibody, bridges activated factor (F)IX and FX, mimicking the cofactor function of activated FVIII and restoring hemostasis in PwHA.

Aims: Measure biomarkers of tissue and joint destruction to understand the effects of emicizumab prophylaxis on joint health.

Methods: Following informed consent and ethics committee approval, PwHA with FVIII inhibitors aged ≥12 years in the Phase 3b Roche-sponsored STASEY study (NCT03191799) received once-weekly 1.5mg/kg maintenance dosing of emicizumab. Serum and plasma samples from 113 PwHA were collected after overnight fasting at baseline, and following 6 months and 2 years of emicizumab. Separately, samples were collected from 20 healthy volunteers (HV). Collagen degradation and formation products were measured using immunoassays against C4M, PRO-C4, PRO-C8, C2M, PRO-C2, and PRO-C18 (Nordic Bioscience). Proteomic analysis of 2926 proteins was performed (Olink). Differences in expression were identified using linear regression and linear mixed model regression, with p-values adjusted for multiple testing (Benjamini-Hochberg).

Results: PRO-C8 (collagen 8 synthesis) was higher in PwHA vs. HV and decreased with emicizumab treatment; PRO-C2 and C2M (collagen 2 markers of cartilage formation and degradation) increased with treatment, indicating cartilage remodeling. Proteomics analysis showed upregulation of inflammatory response, angiogenesis, coagulation and complement pathways in PwHA vs. HV at baseline, and downregulation upon emicizumab treatment. Proteomics also showed upregulation of selected pathways related to osteoporosis, arthropathy, and arthritis in PwHA vs. HV and downregulation upon emicizumab treatment.

Conclusion(s): Proteins linked to biological pathways associated with hemophilic arthropathy were upregulated in PwHA at baseline and downregulated over 2 years of emicizumab prophylaxis, suggesting that emicizumab may positively affect joint health in PwHA with FVIII inhibitors.

Hemoglobin increase in children with hemophilia A on emicizumab: HAVEN 2 & 7 post-hoc analysis (PB0831, ISTH 2025)

G. Batsulil et al

Background: Blood loss in children with hemophilia A (HA) increases risk of iron deficiency and low hemoglobin levels. It is theorized that hemoglobin levels may improve upon initiation of prophylaxis, for example with the bispecific monoclonal antibody emicizumab.

Aims: To assess change from baseline in hemoglobin and associated red blood cell (RBC) indices in children (<12 years old) receiving emicizumab for severe HA during the Roche-sponsored HAVEN 2 and 7 trials.

Methods: Ethics approval and consent were obtained. Change over time in hemoglobin and associated RBC indices were evaluated in the pooled population and in subgroups by age, inhibitor status, and prior treatment regimen.

Results: In the pooled population (N=143), mean hemoglobin (95% confidence interval [CI]) was 119.3 g/L (117.3-121.3) at baseline, increasing to 123.8 (122.0-125.6) at Weeks 49-53 (Figure 1). Similar increases occurred across associated RBC indices. In the youngest participants (<1 month old; n=7), mean hemoglobin (95% CI) was 135.7 g/L (116.1-155.4) at baseline, decreased to 106.9 (97.3-116.4) at Week 4, then increased over time; a decrease during the first months of life is consistent with a normal pattern in infants without hemophilia (Orkin et al. Elsevier Saunders). Subsequently, mean

hemoglobin increased gradually with participants' age. In participants with (n=88) and without (n=55) inhibitors, mean hemoglobin (95% CI) increased from 120.4 (118.1-122.8) and 117.4 (113.8-121.1) g/L at baseline, respectively, to 125.9 (124.1-127.8) and 120.4 (116.9-123.9) at Weeks 49-53. Increased hemoglobin after emicizumab initiation was seen regardless of prior treatment.

Conclusion(s): As in children without hemophilia, hemoglobin levels steadily increased over time in children with severe HA receiving emicizumab prophylaxis. Emicizumab is associated with low bleeding rates in children with HA and, by preventing bleeding, may help mitigate iron-deficiency anemia and/or anemia of chronic inflammation. Studies are warranted to investigate this hypothesis.

The impact of emicizumab on averted bleeds and hospitalisation days in people with haemophilia A (PB0881, ISTH 2025)

M. Arnold et al

Background: Emicizumab is a prophylactic treatment for people with hemophilia A (PwHA), reducing bleeding when compared with factor (F)VIII or bypassing agent (BPA) prophylaxis (Oldenburg, et al. 2017; Mahlangu, et al. 2018).

Aims: This study aims to quantify the population-level impact of emicizumab, relative to treatment with on-demand or prophylactic FVIII replacement/BPAs, on HA disease and associated economic burden. An epidemiological model is used to project clinical and economic outcomes, combining results of clinical trials and epidemiological data along with assumptions on future uptake. Here we focus on the impact of emicizumab in three countries: Greece, Slovenia and France.

Methods: We modelled outcomes associated with emicizumab market introduction and uptake, by comparing a scenario of 'absence of emicizumab' (FVIII replacement/BPAs) versus a scenario of 'introduction of emicizumab'. A comparative analysis of both scenarios quantifies a population-level projected impact per year of switching to emicizumab on: events (bleeds, arthroplasties, disease-related deaths); quality-adjusted life years; direct medical costs associated with bleeds; productivity losses; and indirect costs. This abstract focuses on treatment effectiveness in preventing bleeds over the coming decade in PwHA eligible for emicizumab with or without FVIII inhibitors. Funding for this analysis was provided by F. Hoffmann-La Roche Ltd.

Results: In the coming decade (2025-2034), emicizumab is expected to decrease bleeding in PwHA by 60% (in Greece) to 80% (in Slovenia and France). In France alone, a total of 384,000 bleeds and close to 20,000 hospitalization days could be averted with emicizumab compared with on-demand/prophylactic FVIII replacement/BPAs. Detailed results will be presented in a full report.

Conclusion(s): Results show that emicizumab provides wide-ranging benefits at the population level. Bleeding events experienced by PHA receiving emicizumab versus FVIII replacement/BPAs are projected to diminish by up to 80% in the coming decade, with resultant reductions in hospitalizations and associated costs.

Factor VIII activity in people with mild hemophilia A receiving emicizumab in the HAVEN 6 trial (PB0817, ISTH 2025)

A. Shapiro et al

Background: Some people with mild hemophilia A (HA) (factor [F]VIII activity >5-<40U/dL) have a severe bleeding phenotype and experience long-term effects of bleeding, particularly following joint bleeds. These individuals benefit from prophylactic treatment, although few clinical trials evaluate prophylaxis for mild HA. The HAVEN 6 trial assessed emicizumab in mild and moderate HA; additional information on the use of emicizumab in people with mild HA could address disparities in care, including for women.

Aims: To describe bleeding rates according to endogenous FVIII activity in people with mild HA receiving emicizumab in HAVEN 6.

Methods: The Roche-sponsored Phase 3 HAVEN 6 trial assessed the safety and efficacy of emicizumab in people with non-severe HA without FVIII inhibitors (Négrier, Lancet Haematol 2023). Ethical approval and informed consent were obtained. Investigators determined that all enrolled participants with a diagnosis of mild HA warranted prophylaxis. Mean on-study FVIII levels were derived from all FVIII (bovine) measurements during the study, excluding those drawn within 5 half-lives of receipt of exogenous FVIII.

Results: Overall, 21 people with mild HA enrolled; two were female. Mean (range) FVIII activity (bovine) was 7.98 (3.0-20.8) U/dL, with most (71.4%) participants having a level <10 U/dL. Mean annualized bleed rate (ABR; 95% confidence interval [CI]) for all bleeds in the 24 weeks prior to study entry was 20.2 (12.4, 31.1). After a median (range) of 50.1 (8.1-88.1) weeks on emicizumab, the mean ABR (95% CI) for all bleeds was 2.6 (0.5, 8.1). The mean ABR (95% CI) for on-study treated bleeds was 1.0 (0.02, 5.5). There was no apparent relationship between mean FVIII activity and individual participant ABRs while on emicizumab.

Conclusion(s): Emicizumab was efficacious in people with mild HA enrolled in HAVEN 6, irrespective of FVIII activity. The small sample size limits the conclusions that can be drawn.

Factor VIII inhibitor titers in people with hemophilia A on emicizumab prophylaxis in ATHN 7 (OC15.03, ISTH 2025)

T. Chrisentery-Singleton et al

Background: In clinical trials of emicizumab, factor (F)VIII inhibitor titers remained stable or decreased in people with hemophilia A (PwHA) with inhibitors at study baseline. In the Phase 3/3b trials of PwHA without inhibitor at baseline, 0/191 participants in HAVEN 3 and 4 (final analysis; Mahlangu, RPTH 2024) and 2/55 participants in HAVEN 7 (primary analysis; Pipe, Blood 2024) developed a de novo inhibitor while on emicizumab.

Aims: To report real-world data on FVIII inhibitor titer and de novo inhibitor development in PwHA receiving emicizumab in the ATHN 7 study (NCT03619863).

Methods: ATHN 7 was conducted across 26 American Thrombosis and Hemostasis Network-affiliated sites (partially supported by Genentech). IRB approval and consent were obtained. PwHA receiving emicizumab were eligible for this analysis. Inhibitor testing was carried out at study entry, annually, and in cases of suspected inhibitor development.

Results: Overall, 257 participants enrolled in ATHN 7 received emicizumab; the median (min, max) emicizumab exposure was 116.4 (0.1, 206.6) weeks at data cut-off (Apr 30, 2024). In total, 63/257 (24.5%) participants had FVIII inhibitor at study entry. For participants with titer measurements available at both emicizumab initiation and data cut-off (N=38), median titer remained relatively constant, from 1.00BU (Q1-Q3: 0.2-4.0) to 0.35BU (0.0-1.1). For PwHA without inhibitors at study entry (N=191), there was one report of transient de novo inhibitor development. This was a male infant aged 1 year at study entry, who had 40 FVIII exposure days recorded during emicizumab treatment. He had a number of positive inhibitor tests (max. titer: 1.60BU), with the titer subsequently decreasing to 0.30BU at the latest measurement.

Conclusion(s): In PwHA, FVIII inhibitor titers remained stable from emicizumab initiation to data cut-off. There was one case of de novo inhibitor development, associated with FVIII exposure. These real-world data are consistent with those from clinical trials.

Efficacy, safety and satisfaction of using emicizumab in hemophilia A patients without factor VIII inhibitors: A systematic review (Hematology, Transfusion and Cell Therapy 2025)

I. de Oliveira Araujo et al

Background: Haemophilia A is a genetic disorder characterized by deficiency or dysfunction of the factor VIII clotting protein, leading to serious bleeding disorders. Conventional treatment involves the exogenous administration of factor VIII. However, this therapy faces significant challenges, including the development of inhibitors and the need for frequent intravenous administration. Emicizumab, a recombinant bispecific monoclonal antibody that can be administered subcutaneously, offers a novel therapeutic alternative by mimicking the action of factor VIII.

Methods: This systematic review evaluates the efficacy, safety, and patient satisfaction with emicizumab in patients with hemophilia A without inhibitors. A comprehensive literature search was conducted using the MEDLINE, SciELO, and LILACS databases. The included studies were original articles on the use of emicizumab in hemophilia A patients without inhibitors and reviews, short communications, expert comments, and case reports were excluded. Data extraction and analysis were performed using predefined criteria.

Results: A total of 471 articles were identified, with 28 meeting the inclusion criteria. Studies demonstrated robust evidence of the efficacy of emicizumab in reducing bleeding episodes, with significant reductions in the Annualized Bleeding Rate and Annualized Joint Bleeding Rate. Safety profiles were favorable, with mainly minor adverse events reported. High patient satisfaction scores highlighted improvements in quality of life and treatment adherence.

Conclusion: Emicizumab represents a significant advancement in hemophilia A treatment, offering superior efficacy, safety, and patient satisfaction compared to traditional therapies. Future research should focus on long-term outcomes and specific subpopulations to further validate these findings.

NXT007

Insights from *in vitro* global assays on possible doses of concomitant hemostatic agents in the presence of NXT007 in haemophilia A (PubMed 2025)

K. Ogiwara et al

Background: Concomitant administration of activated prothrombin complex concentrate (APCC) at doses >100 U/kg/d is associated with thrombotic risk under emicizumab prophylaxis. *In vitro* global assay data on the effects of concomitant coagulation factor agents in the presence of NXT007, an emicizumab-based engineered bispecific antibody under clinical development, may serve as a basis for addressing this potential risk.

Objectives: This study aimed to investigate the *in vitro* effects of recombinant factor (rF)VIII, rFVIIa, and APCC during NXT007 treatment and estimate tolerable doses with reference to emicizumab.

Methods: Thrombin generation assays, clot waveform analysis, and rotational thromboelastometry were performed using hemophilia A plasma and blood samples spiked with NXT007 and others.

Results: A single dose of NXT007 at ≥10.0 μg/mL (plasma) achieved a nonhemophiliac coagulation potential. The concomitant addition of rFVIII, rFVIIa, and APCC each boosted various parameters following NXT007 levels at 0.1 to 50.0 μg/mL. In the copresence of NXT007 at 15.0 μg/mL (blood) and APCC at 0.13 U/mL, with the blood level immediately following the administration of 10.0 U/kg, the rotational thromboelastometry parameters were comparable with those observed with clinical emicizumab level and APCC at 0.63 U/mL, corresponding to the blood level immediately after administrating 50.0 U/kg (recommended initial dose).

Conclusions: A single dose of NXT007 at ≥10.0 μg/mL (plasma) achieved a nonhemophiliac coagulation potential. The concomitant addition of rFVIII, rFVIIa, and APCC each boosted various parameters following NXT007 levels at 0.1 to 50.0 μg/mL. In the copresence of NXT007 at 15.0 μg/mL (blood) and APCC at 0.13 U/mL, with the blood level immediately following the administration of 10.0 U/kg, the rotational thromboelastometry parameters were comparable with those observed with clinical emicizumab level and APCC at 0.63 U/mL, corresponding to the blood level immediately after administrating 50.0 U/kg (recommended initial dose).

Results: Overall, 28 PwSHA enrolled, all male [median age: 26.5 (range: 12-52) years; median observation time: 50 weeks). Most (12/18) CATCH domain scores were <25 at baseline and remained stable, indicating low bleed risk perception. Treatment burden improved by a mean (standard deviation; % change) of 17.8 (21.1; 55.7%) for adults and 16.7 (15.5; 33.4%) for adolescents from baseline to Week 49. IPAQ-SF scores for moderate/vigorous activity were stable throughout. Mean daily step counts were similar [7982 (NIS) vs. 8619 (HemiNorth 2)]. EmiPref indicated that 23/25 (92.0%) respondents preferred emicizumab over FVIII prophylaxis. From the NIS to HemiNorth 2, model-based ABRs [95% confidence interval (CI); median observation time] for treated bleeds decreased from 5.9 (3.7-9.4; 27 weeks) to 1.6 (0.8-3.2; 48 weeks); participants with zero treated bleeds increased from 8 (28.6%) to 16 (57.1%). A sensitivity analysis performed to exclude one

participant (due to low treatment compliance in the NIS) was consistent. One participant reported three serious AEs (deemed unrelated to emicizumab).

Discussion/Conclusion: Emicizumab reduced treatment burden and was preferred over FVIII prophylaxis. PA levels and daily step counts were consistent throughout. Bleeding rates decreased and the number of participants with zero bleeds increased despite consistently high PA. There were no new safety signals.

NXT007 Prophylaxis in Emicizumab-Naive Persons with Hemophilia A without Inhibitor: Phase I/II Study (OC 20.3, ISTH 2025)

C. You et al

Background: 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. The tolerability and pharmacokinetics of a single dose of NXT007 in healthy adults have been presented, and this is the first presentation of clinical data of NXT007 in persons with hemophilia A (PwHA).

Aims: To report primary analysis results from phase I/II study evaluating the safety, pharmacokinetics, and efficacy of NXT007 in PwA (NXTAGE; JapicCTI-194919).

Methods: In this multiple ascending dose study, emicizumab-naïve PwHA without FVIII inhibitors aged =12 years and <65 years were eligible and enrolled to 4 cohorts (B-1 to B-4). Participants received subcutaneous maintenance doses (MD) of NXT007 every 2 or 4 weeks after 4- to 6-week loading doses. NXTAGE study was conducted in accordance with the principles of the Declaration of Helsinki, and all relevant laws and regulations of Japan, Taiwan, and South Korea.

Results: Thirty participants were enrolled (Cohorts B-1 [n=10], B-2 [n=6], B-3 [n=6], B-4 [n=8]), and the average treatment period of each cohort was 104, 100, 61 and 20 weeks, respectively. Two participants were withdrawn from the study. NXT007 was well tolerated with no thromboembolic events. During MD period, 9 participants in B-1, 3 participants in B-2, 1 participant in B-3, and 2 participants in B-4 experienced =1 all bleeds (untreated and treated bleeds). Participants in B-3 and B-4, for whom >40 U/dL of equivalent FVIII activity is predicted to be kept, did not experience any treated bleeds during MD period. No participants showed a remarkable increase of D-dimer after NXT007 administration.

Conclusion(s): These results suggest that NXT007 has a potential to provide a non-hemophilic range of coagulation activity in PwHA with tolerable safety profile, supporting the transition to next phase clinical studies.

Inno8

In vitro activity of Inno8 in global hemostatic assays alone and with other hemostatic agents (OC 39.2, ISTH 2025)

Background: Inno8 is a novel FVIIIa mimetic molecule composed of VHH domains binding FX and FIXa, designed with high in vitro potency and intended for oral prophylactic treatment of hemophilia A (HA) with and without FVIII-inhibitors using the SNAC absorption enhancer. Understanding how

Inno8 functions in global hemostatic assays alone or in combination with hemostatic agents is important for future clinical use.

Aims: Characterization of Inno8 in vitro hemostatic activity in global assays alone or in combination with hemostatic agents used for management of HA.

Methods: Thrombin generation kinetics assessed in HA-like platelet poor plasma (PPP) and platelet-rich plasma PRP), both prepared from healthy donor plasma supplemented neutralizing anti-FVIII antibody, using both 1 pM tissue factor (TF) and 8 mU/mL FXIa triggers. Thromboelastography was performed in FVIII-neutralized whole blood from healthy subjects using recalcification. Effect of combining Inno8 with relevant clinical dose of FVIIa, FVIII, aPCC and FVIIIa mimetics on thrombin generation in congenital HA plasma was assessed in vitro using 1 pM TF as trigger.

Results: Inno8 increased peak thrombin in a concentration dependent manner in both induced-HA PPP and PRP with EC50 values of 10.1 (PPP) and 3.4 nM (PRP) with TF trigger and 0.3 (PRP) to 1.3 nM (PPP) with FXIa trigger. Similarly, Inno8 increased in a concentration dependent manner the a-angle in thromboelastography with recalcification (EC50 1.1 nM). Inno8 did not interfere with FVIIIa function. Supplementing 10 nM Inno8 with FVIIa, FVIII, Mim8 and emicizumab-SIA increased thrombin peak within normal levels. Like for other FVIIIa mimetics, combination with aPCC increased thrombin peak above normal levels.

Conclusion(s): Inno8 increased thrombin generation and clot formation in a concentration dependent manner in HA-like blood and plasma reaching normal levels at concentrations of 10 nM. Interactions with haemostatic agents were similar to those described for other FVIIIa mimetics.

Factor Replacement Therapies

Efanesoctocog alfa (Altuvoct, Altuviiio)

Long-term outcomes of prophylaxis with efanesoctocog alfa in adults and adolescents previously treated on demand: second interim analysis of XTEND-ed (PP-44 2009654), WFH 2025)

V. Jimenez-Yuste et al

Introduction: Efanesoctocog alfa is a first-in-class high-sustained (also called ultra-long half-life) factor VIII (FVIII) replacement therapy designed to decouple FVIII from endogenous von Willebrand factor. In the Phase 3 XTEND-1 study (NCT04161495), once-weekly efanesoctocog alfa demonstrated superior bleed protection over prior FVIII prophylaxis, was well tolerated, and provided FVIII activity within the normal to near-normal (>40%) range for most of the week. We present long-term safety and efficacy data from adults with severe haemophilia A who switched from on-demand to weekly prophylactic efanesoctocog alfa therapy in the XTEND-1 study and continued prophylactic treatment in the XTEND-ed study (NCT04644575).

Methods: Patients who received 26 weeks of on-demand treat-ment, followed by 26 weeks of weekly prophylaxis in XTEND-1 (Arm B), could continue efanesoctocog alfa (50 IU/kg, once-weekly)

prophylaxis in the multicentre, open-label, long-term XTEND-ed study. The primary endpoint is incidence of FVIII inhibitor development. Secondary endpoints include annualised bleed rates (ABRs), haemophilia joint health score (HJHS) and safety. Second interim data cut: 22 February 2024.

Results: Overall, 25/26 males treated with prior on-demand efanesoctocog alfa in XTEND-1 (age 18-64 years, n = 25; ≥65 years, n = 1) enrolled into XTEND-ed. Mean (standard deviation [SD]) weekly prophylactic dose was 51.12 (1.76) IU/kg. No FVIII inhibitors were detected. Mean (SD) ABRs during XTEND-ed were 0.49 (1.20 [Day 1-Month 6, n = 25]), 0.34 (0.80 [Months 6-12, n = 24]), 0.35 (0.80 [Months 12-18, n = 23]), and 0.36 (0.80 [Months 18-24, n = 23]), with 21/25 (84.0%), 20/24 (83.3%), 19/23 (82.6%), and 19/23 (82.6%) patients with zero bleeds, respectively. Thirteen (52.0%) patients experienced ≥1 treatment-emergent adverse events (TEAE); most common were falls (16.0%) and viral infections (16.0%). Three patients (12.0%) experienced ≥1 serious TEAE, including one patient with a femur fracture who discontinued because of use of a prohibited concomitant medication.

Conclusions: The improvements in ABR and HJHS observed for previously treated on-demand patients switching to prophylaxis during XTEND-1 were maintained in XTEND-ed. Efanesoctocog alfa was well tolerated and no inhibitors were detected.

Efanesoctocog Alfa versus Standard and Extended Half-Life Factor VIII Prophylaxis in Adolescent and Adult Patients with Haemophilia A without Inhibitors (Springer 2024)

R. Klamroth et al

Introduction: In the Phase 3 XTEND-1 trial, (NCT04161495) efanesoctocog alfa prophylaxis provided superior bleed protection versus pre-study factor VIII (FVIII) replacement therapy in patients with severe haemophilia A. The aim of this study was to indirectly compare bleed outcomes between efanesoctocog alfa and standard/extended half-life (SHL and EHL) FVIII replacement therapies in adolescent and adult patients with severe haemophilia A without inhibitors.

Methods: A systematic literature review was conducted to identify Phase 3 trials of EHL and SHL FVIII replacement therapies for comparison with efanesoctocog alfa data from XTEND-1. Matching-adjusted indirect comparisons were used to compare annualised bleeding rates (ABRs) for any, treated, joint, and spontaneous bleeds between efanesoctocog alfa and comparators. The estimates from respective comparisons were pooled using random-effect meta-analyses to evaluate the overall difference between efanesoctocog alfa and comparator therapies.

Results: Four EHL therapies (rurioctocog alfa pegol, efmoroctocog alfa, turoctocog alfa pegol, damoctocog alfa pegol) and two octocog alfa SHL therapies were included. In meta-analyses, efanesoctocog alfa was associated with significantly lower ABRs for any [mean difference (95% CI) – 2.24 (– 3.24; – 1.25)], spontaneous [– 1.52 (– 2.33; – 0.72)], and joint bleeds [– 1.60 (– 2.32; – 0.88)] versus EHL therapies, and with significantly lower ABRs for any [– 3.61 (– 4.43; – 2.79)], treated [– 1.55 (– 1.89; – 1.20)], spontaneous [– 2.52 (– 3.31; – 1.72)], and joint bleeds [– 3.42 (– 4.77; – 2.08)] versus SHL therapies.

Conclusion: Efanesoctocog alfa was associated with significantly lower ABRs (any, spontaneous and joint) compared with EHL or SHL prophylaxis therapies. Patients had, on average, 2.2 and 3.6 fewer bleeds per year versus EHL and SHL therapies, respectively.

Efanesoctocog Alfa Versus Emicizumab in Adolescent and Adult Patients With Haemophilia A Without Inhibitors (Springer 2024)

M. T. Á. Román, N. Kragh et al

Introduction: The phase 3 XTEND-1 trial (NCT04161495) demonstrated that efanesoctocog alfa prophylaxis provided superior bleed protection compared with pre-trial factor VIII (FVIII) prophylaxis in patients with severe haemophilia A. The aim of this study was to indirectly compare the efficacy of efanesoctocog alfa with non-factor replacement therapy emicizumab in adolescent and adult patients with severe haemophilia A without inhibitors.

Methods: A systematic literature review was conducted to identify phase 3 trials of emicizumab. Matching-adjusted indirect comparisons were used to compare annualised bleeding rates (ABRs) for any, treated, joint, and spontaneous bleeds, and joint health (measured using Hemophilia Joint Health Score [HJHS]), between efanesoctocog alfa and emicizumab. Estimated effects for different emicizumab regimens were pooled using random-effect meta-analysis to evaluate the overall difference in bleed outcomes between efanesoctocog alfa and emicizumab.

Results: One emicizumab trial was included (HAVEN 3), which investigated three dosing regimens. In meta-analyses, efanesoctocog alfa once-weekly (Q1W) was associated with significantly lower ABRs for any (incidence rate ratio [95% CI] 0.33 [0.20; 0.53]), any treated (0.49 [0.30; 0.80]) and treated joint (0.51 [0.28; 0.91]) bleeds compared with emicizumab Q1W in non-inhibitor patients with prior prophylaxis or on-demand treatment. Efanesoctocog alfa Q1W was also associated with a significantly better improvement from baseline in HJHS Joint Score (mean difference [95% CI] −2.06 [−3.97; −0.14]) and Total Score (−2.37 [−4.36; −0.39]) versus emicizumab Q1W or every 2 weeks.

Conclusion: Efanesoctocog alfa prophylaxis was associated with significantly lower rates of any, treated, and joint bleeds and improved joint health compared with emicizumab in patients with severe haemophilia A.

Treatment of Bleeding Episodes With Efanesoctocog Alfa in Previously Treated Patients With Severe Hemophilia A in the Phase 3 XTEND-1 Study (Wiley 2025)

A. C. Weyand et al

Abstract: Despite therapeutic advances, people with hemophilia experience bleeds. These may be life-threatening, result in permanent joint damage, chronic pain, difficulties with mobility/daily activities, and impact quality of life. In the XTEND-1 study (NCT04161495), once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis provided highly effective bleed prevention and high-sustained factor levels for most of the week and was well-tolerated. We report post hoc analysis of bleeding episodes and their treatment in previously treated patients (≥ 12 years old). Participants received 50 IU/kg efanesoctocog alfa either as once-weekly prophylaxis (Arm A) or on-demand followed by once-weekly prophylaxis (Arm B) in XTEND-1. Endpoints included treatment of bleeding episodes and response to treatment. During XTEND-1, 422 bleeding episodes were reported among 159 participants; 362 were treated. Most treated bleeding episodes (74%; $n = 268$) occurred during the Arm B on-demand period, of which 197 (74%) were spontaneous. Seventy-five participants had no bleeding episodes in Arm A; all in Arm B had ≥ 1 bleeding episode while on-demand. Most participants ($n = 107$, 81%) had zero treated spontaneous bleeding episodes and rates of treated

bleeding episodes in Arm A (prophylaxis) were low (median [interquartile range] overall ABR: 0.00 [0.00–1.04]). A single injection was sufficient to resolve 97% (350/362) of treated bleeding episodes, no bleeding episodes required > 3 injections, and responses to 95% of evaluable injections were rated excellent/good. Median total dose was 50.9 IU/kg per bleeding episode. Results of this analysis further demonstrated that once-weekly efanesoctocog alfa provides highly effective bleed protection and treatment of bleeding episodes in participants with severe hemophilia A.

Efanesoctocog Alfa Population Pharmacokinetics and Repeated Time-To-Event Analysis of Bleeds in Adults, Adolescents, and Children with Severe Hemophilia A (ACCP 2025)

N. Wong et al

Abstract: Efanesoctocog alfa is a first-in-class high-sustained factor VIII (HSF) replacement therapy for treatment of hemophilia A. This article presents population pharmacokinetics (PopPK) of efanesoctocog alfa and repeated time-to-event (RTTE) analysis of bleeding episodes in adults/adolescents (≥12 years of age) and children (<12 years). The final PopPK dataset contained pooled data from 277 patients (4405 post-dose factor VIII [FVIII] activity records) from two Phase 1/2a studies (NCT03205163; EudraCT 2018-001535-51), and three Phase 3 studies, XTEND-1 (NCT04161495), XTEND-Kids (NCT04759131), and XTEND-ed (NCT04644575). The PopPK model developed was a linear one-compartment model including body weight effect on clearance and volume of central compartment; Asian race was identified as a statistically significant covariate on clearance. The final PopPK model adequately described the FVIII activity–time profiles in adults, adolescents, and children with once-weekly (QW) efanesoctocog alfa 50 IU/kg, consistent with experience in XTEND-1 and XTEND-Kids. Bleeding episodes in participants in XTEND-1 and XTEND-Kids were characterized by an RTTE model with a Weibull base hazard and effect of FVIII activity modeled by a power effect. The RTTE model showed the probability of being bleed-free in 1 year with efanesoctocog alfa 50 IU/kg QW regimen was >70% across all age groups, consistent with the observed clinical outcomes in the Phase 3 trials of highly effective protection from bleeding episodes in patients with severe hemophilia A, which validates the model's prediction of the long-term bleed hazard.

Perioperative Management With Efanesoctocog Alfa in Patients With Haemophilia A in the Phase 3 XTEND-1 and XTEND-Kids Studies (Wiley 2025)

R. Klamroth et al

Introduction: The Phase 3 studies, XTEND-1 (NCT04161495) and XTEND-Kids (NCT04759131), showed once-weekly efanesoctocog alfa provided high-sustained factor VIII (FVIII) activity levels that translated into highly effective bleed prevention in patients with severe haemophilia A.

Aim: This analysis evaluated the efficacy and safety of efanesoctocog alfa for perioperative management during XTEND-1 and XTEND-Kids.

Methods: Patients undergoing major or minor surgery were to receive a single preoperative 50 IU/kg dose, with additional 30 or 50 IU/kg doses every 2–3 days as needed following major surgery. Outcomes assessed included FVIII activity levels, number and dose of efanesoctocog alfa injections, surgeon's/investigator's assessment of haemostatic response, total factor consumption, estimated blood loss, number and type of blood transfusions, and safety.

Results: In XTEND-1, 11 adults/adolescents underwent 12 evaluable major surgeries (6 orthopaedic). Eleven surgeries had one preoperative dose (median [range]: 49.9 [13–52] IU/kg); one had no preoperative dose. Median (range) total consumption from Day −1 to 14 was 163.3 (45–361) IU/kg. In XTEND-Kids, two children underwent major surgery with a single preoperative loading dose (60.4 and 61.9 IU/kg). Across trials, 15 adults/adolescents underwent 18 minor surgeries and 8 children underwent 9 minor surgeries, with a single preoperative dose or no preoperative dose (5 surgeries in adults/adolescents). Haemostatic response was rated excellent for all surgeries. No surgeries required blood transfusion. No safety concerns or inhibitor development was reported.

Conclusion: Efanesoctocog alfa provided highly effective perioperative protection in patients with severe haemophilia A.

Pharmacokinetic evaluation of efanesoctocog alfa: breakthrough factor VIII therapy for hemophilia A (Taylor & Francis 2025)

K. Yada et al

Introduction: Blood coagulation factor (F)VIII functions as a cofactor in the tenase complex responsible for phospholipid-dependent FIXa-mediated activation of FX in plasma. Congenital defect of FVIII causes severe bleeding disorder, hemophilia (H) A. Intravenous FVIII replacement therapy is the gold standard therapy in patients with HA (PwHA) but requirement for frequent dosing of FVIII owing to pharmacokinetics burdens PwHA a lot. Efanesoctocog alfa is a new class of recombinant FVIII and has the ability to overcome conceivable unmet needs in treatment for PwHA.

Areas covered: Efanesoctocog alfa is a B domain-deleted single-chain fusion FVIII connected to the Fc-region of human immunoglobulin G1, D'D3-fragment of von Willebrand factor (VWF), and unstructured hydrophilic recombinant polypeptides (XTEN). Owing to its novel design, it can function independently of endogenous VWF and elicits 2 to 4 times longer half-life compared to other existing FVIII products. The prolonged half-life contributes to maintaining a high level of FVIII activity for most of the week and has led to excellent hemostatic effect by once-weekly administration in phase 3 clinical trials.

Expert Opinion: Efanesoctocog alfa with outstanding pharmacological properties, well tolerated in the clinical trials, is a promising FVIII therapy for PwHA. Future studies should include long-term safety, especially in previously untreated patients.

Accurate evaluation of factor VIII activity of efanesoctocog alfa in the presence of emicizumab (PubMed 2025)

C. Nougier, S. W. Pipe et al

Background: Efanesoctocog is a B-domain-deleted, Fc-fusion factor (F)VIII linked to the D'D3 domain of von Willebrand factor and 2 XTEN polypeptides, designed for an ultra-extended half-life for prophylaxis in hemophilia A, but also aiding in managing acute bleeding or surgery in patients on long-term emicizumab. However, no current laboratory method accurately measures FVIII levels in the presence of emicizumab.

Objectives: To test whether the bovine chromogenic FVIII assay, specifically calibrated for efanesoctocog, could provide an accurate assessment of efanesoctocog activity.

Methods: Seven centers across 5 countries received 12 plasma samples to measure in triplicate using 2 calibration methods across 3 independent days. Samples (n = 6) contained either only efanesoctocog (FVIII activity [FVIII:C]= 5 to 150 IU/dL), or efanesoctocog (FVIII:C = 5 to 150 IU/dL) in combination with emicizumab (50 μg/mL; n = 5). One sample contained efanesoctocog (FVIII:C = 50 IU/dL) and a high dose of emicizumab (80 μg/mL); another sample contained efanesoctocog (FVIII:C = 50 IU/dL) with a low dose of emicizumab (20 μg/mL). Each center used its own analyzers, along with their usual reagents.

Results: Chromogenic assay (CSA) calibrated with standard calibrators highly overestimates FVIII:C. However, specific calibration with efanesoctocog enabled accurate measurement of FVIII:C, with low inter- and intra-laboratory variability, and no interference from emicizumab. All CSA reagents used in the study demonstrated low variability across different laboratories (interlaboratory coefficient of variation ranges between 9% and 20%).

Conclusion: Specific calibration of the FVIII CSA using efanesoctocog and bovine reagents allows for accurate measurement of FVIII:C in patients receiving efanesoctocog, even in the presence of emicizumab.

Treatment of Bleeding Episodes with Efanesoctocog Alfa in Adults and Adolescents with Severe Haemophilia A: Second Interim Analysis of the XTEND-ed Long-term Extension Study (PO060, EAHAD 2025)

J. Oldenburg et al

Introduction: Efanesoctocog alfa is a first-in-class high-sustained Factor VIII replacement therapy that overcomes the von Willebrand factor-imposed half-life ceiling. XTEND-1 (NCT04161495) showed once-weekly efanesoctocog alfa was well tolerated in adults/adolescents with severe haemophilia A providing superior bleed prevention over prior FVIII prophylaxis. XTEND-ed (NCT04644575) evaluates long-term safety and efficacy of efanesoctocog alfa. We report bleeding events (BEs) in adults/adolescents from the 2nd interim analysis of XTEND-ed.

Methods: Previously treated patients (aged ≥12 years) who completed XTEND-1 could continue once-weekly efanesoctocog alfa prophylaxis (50 IU/kg) in XTEND-ed. BEs were treated with single-dose efanesoctocog alfa (50 IU/kg) and further doses (30 or 50 IU/kg) as needed every 2-3 days. The number and location of treated BEs were recorded with the dose and number of injections required for resolution. Annualised bleeding rates (ABRs) were derived from a negative binomial model of treated BEs. Participants scored treatment response at 72 h post-treatment using the International Society for Thrombosis and Haemostasis scale. Data cut: 22 February.

Results: Overall, 146 participants rolled over from XTEND-1 to XTEND-ed (age: 12-17 years, n = 21; 18-64, n = 120; ≥65, n = 5). At data cutoff, 10 participants discontinued the study, 11 completed and 125 were ongoing. Mean (range) treatment duration in XTEND-ed was 116.1 (14.1-140.6) weeks. Mean (range) exposure was 116.5 (14-147) days. Mean (95% CI) model-based ABRs during XTEND-ed were: overall 0.64 (0.50, 0.82); spontaneous 0.23 (0.16, 0.32); traumatic 0.32 (0.23, 0.43); unknown 0.08 (0.05, 0.15); joint 0.45 (0.33-0.62). There were 205 treated BEs in 146 participants over >2 years'

follow-up, most commonly in joints (39.0%) and muscles (17.1%). A single efanesoctocog alfa injection resolved 94.6% of BEs; 11 required ≥2 injections. Median (IQR) efanesoctocog alfa total dose for resolution was 50.3 (32.3- 51.7) IU/kg. Responses were rated good or excellent for 86.9% of BES.

Discussion/Conclusion: Long-term data from the 2nd interim analysis of XTEND-ed show that in previously treated adults and adolescents with severe haemophilia A, a single 50 IU/kg dose of efanesoctocog alfa continues to provide highly effective treatment of BEs regardless of type or location.

Rurioctocog Alfa Pegol

Phase 3 Study of Rurioctocog Alfa Pegol in Previously Untreated Patients with Severe Hemophilia A (LB 01.2, ISTH 2025)

R. Sidonio et al

Background: Factor VIII (FVIII) replacement therapy for hemophilia A (HA) can result in FVIII inhibitors, a serious complication that may require immune tolerance induction (ITI). In previously untreated patients (PUPs), inhibitor incidence is approximately 30%.

Aims: To assess the safety, immunogenicity, and hemostatic efficacy of rurioctocog alfa pegol (rAHF-PEG), an extended half-life recombinant FVIII, in PUPs.

Methods: This phase 3, prospective, open-label, multicenter trial (NCT02615691) included PUPs aged <6 years with severe HA (FVIII <1%). Interim results (≥50 exposure days [EDs]) were previously reported. Exclusion criteria included current or historical FVIII inhibitors. Patients received prophylactic or on-demand rAHF-PEG. The primary outcome was FVIII inhibitor (≥0.6 BU/mL) development; secondary objectives included safety and hemostatic efficacy. Patients with confirmed inhibitors were eligible for ITI therapy, with success rate as an additional primary end point. Informed consent and ethics board approval were obtained.

Results: Of 146 screened patients, 120 received ≥1 dose of rAHF-PEG (median [range] age: 0.8 [0.1-5.0] years). Eleven (11%) of 100 patients with ≥100 rAHF-PEG EDs developed confirmed FVIII inhibitors (low titer [≥0.6-5 BU/mL]: n=5; high titer [>5 BU/mL]: n=6) (Table 1); seven underwent IT| with rAHF-PEG. IT| was successful in five patients (success rate: 71%) and partially successful in one. Annualized bleeding rate was lower in patients receiving rAHF-PEG prophylaxis versus on-demand treatment (Table 2). Most on-study bleeds resolved following 1-2 rAHF-PEG infusions, with excellent or good hemostatic efficacy ratings. Aside from 18 treatment-related adverse events (AEs), including FVIII inhibitor development (n=11), AEs were generally treatment-unrelated, and mild or moderate.

Conclusion(s): This is the first study evaluating rAHF-PEG in PUPs with severe HA. Inhibitor incidence was lower than in other studies in PUPs. These findings demonstrate safety and efficacy of rAHF-PEG for prophylaxis, on-demand treatment, and its potential for ITI. Funding: Takeda Pharmaceuticals U.S.A., Inc.

Gene Therapy

Platelet-Targeted Gene Therapy for Hemophilia A with Inhibitor History (The New England Journal of Medicine, 2025)

M. Eapen et al

Abstract: Factor VIII gene was introduced into hematopoietic stem cells in men with hemophilia. The annualized bleeding rate went from 10 to 0. No worrisome gene integrations were seen.

Genomic integration of FVIII transgene in hepatocytes restores durable FVIII activity in vivo (OC 51.2, ISTH 2025)

J. Lund et al

Background: First generation AAV-based gene therapies are approved for the treatment of congenital hemophilia A (HA), however in most instances FVIII plasma levels have been observed to decline over time. Reasons from loss or silencing of the vector to endoplasmic reticulum stress have been proposed to explain the declining expression levels. Genomic integration of a FVIII transgene into a safe harbor locus, facilitated by a site-specific nuclease, may improve durability of FVIII expression potentially curing patients with HA.

Aims: The aim was to develop a durable, in vivo genome editing treatment for patients with HA.

Methods: A site-specific megaTAL endonuclease was engineered to target the first intron of the albumin gene and delivered to hepatocytes as lipid nanoparticle (LNP)-encapsulated mRNA. An AAV vector donor encoding a promoter-less, B-domain truncated FVIII transgene was optimized to enable FVIII expression following targeted integration. In vivo efficacy and tolerability were evaluated in F8-/-/Rag2-/- mice and cynomolgus monkeys following simultaneous treatment with both components.

Results: Following simultaneous administration of AAV donor vector and LNP-encapsulated, murine specific megaTAL mRNA in a F8-I-/Rag2-/- HA mouse model, hepatic expression of human FVIII was induced within days of treatment rescuing the bleeding phenotype following tail vein transection. The specific activity was comparable to recombinant FVIII and the plasma level was proportional to the level of genomic integration which was in turn directly dependent on nuclease-mediated cutting activity at the target locus. In cynomolgus monkey, treatment with surrogate AAV encoding a cynomolgus FVIII B-domain truncated transgene and an optimized megaTAL nuclease resulted in genomic integration in single digit percent of the liver cells and a fast onset of FVIII expression durable for at least 12 weeks averaging 104 IU/dL (n=4).

Conclusion(s): Targeted genomic integration of FVIII transgene has shown promise in pre-clinical models with the potential to become a durable cure for the disease.

Valoctocogene Roxaparvovec (Roctavian)

Variability In FVIII Transgene Expression Among Patients Treated With Valoctocogene Roxaparvovec (PB0886, ISTH 2025)

A. Ciavarella et al

Background: Gene therapy has recently emerged as a transformative treatment option in clinical practice. This report provides real-world data on three patients with severe hemophilia A treated with valoctocogeneroxaparvovec following its approval and commercial availability in Italy.

Aims: To evaluate factor (F)VIII transgene expression and its trend among individuals associated with clinical manifestation.

Methods: Three adult patients (aged ≥18 years) with severe hemophilia A (FVIII ≤1 IU/dL) were referred to the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center in Milan, Italy. These patients were previously on prophylaxis with FVIII extended half-life products and emicizumab. None of them had a history of inhibitors or anti-AAV5 antibodies, and all were free from significant liver dysfunction, fibrosis, or cirrhosis at baseline. Plasma FVIII activity was measured using chromogenic and one-stage assays. FVIII antigen levels were determined using VisuLize Factor VIII antigen Plus kit.

Results: To date, three patients (median age: 36 years) have received a single infusion of 6x1013 vg/kg valoctocogeneroxaparvovec. No allergic reactions were reported. Median follow-up was 26 weeks; all three participants completed 18 weeks. FVIII transgene expression became detectable within three weeks in all patients with a median FVIII activity of 9 IU/dL (chromogenic assay) and a median FVIII antigen level of 7 IU/dL. However, interindividual variability in FVIII activity over time was noted. Detailed transgene expression and antigen levels for each patient at various time points are reported in the table. No significant changes in liver enzyme levels were observed in two patients. However, one patient exhibited elevated alanine aminotransferase levels at week 7, for whom immunosuppressive therapy is ongoing.

Conclusion(s): Real-world experience with patients treated with valoctocogeneroxaparvove has demonstrated successful discontinuation of prophylaxis in all patients three weeks after infusion. Chromogenic activity levels correlated with the total expressed FVIII protein, as quantified by antigen levels. Notably, significant interindividual variability in FVIII transgene expression was observed, underscoring the need for individualized monitoring and management strategies.

Valoctocogene Roxaparvovec Estimated Long-Term Durability of Treatment Effect: An Extrapolation of the Most Recent Clinical Data (PO063, EAHAD 2025)

S. Harris et al

Introduction: Valoctocogene roxaparvovec is a single- administration AAV5-mediated gene therapy that enables endogenous FVIII production to prevent bleeding in people with severe haemophilia A (PwSHA). In the Phase 3 GENEr8-1 study, valoctocogene roxaparvovec demonstrated a higher probability of being bleed free, improvements in annualised bleeding rates (ABR) and in health-related quality of life (HRQOL) 4 years after infusion when compared with outcomes while on FVIII

prophylaxis during the baseline period. The aim of this analysis was to estimate the long-term durability of valoctocogene roxaparvovec treatment effect by extrapolating the most recent trial data (GENEr8-1 4-5-year and 270-201 7-year data).

Methods: Durability was analysed within a time-to-event analysis framework, which is commonly used to extrapolate observed data. The quantity of interest was the rate at which patients experienced loss of response. In alignment with the WFH guidelines and label recommendations, and to reflect the benefit of the treatment as a whole, loss of response was defined in the primary analysis as a clinical overview of an objectively measurable biomarker (FVIII levels <5%), clinical endpoints (≥2 treated bleeds in 6 months) and the return to continuous prophylaxis. The primary analysis used GENEr8-1 data only. Scenario analyses were explored, where other definitions of loss of response were considered, as well as 270-201 7-year data used.

Results: In the primary analysis, the median durability of treatment effect is estimated to range from 11.0-17.0 years. In the scenario where 270-201 data were also used for the extrapolation, the median estimated durability is estimated to range from 13.2 to 20.4 years.

Discussion/Conclusion: This analysis demonstrates that the observed therapeutic benefit is expected to be sustained beyond the 7 years of follow-up in existing clinical trials, illustrating the full treatment benefit that valoctocogene roxaparvovec can bring to PwSHA.

Dirloctocogene Samoparvovec

Pharmacodynamics and pharmacokinetics of dirloctocogene samoparvovec in people with severe to moderately severe haemophilia A (OR03, EAHAD 2025)

L. George et al

Introduction: Dirloctocogene samoparvovec is a low-dose investigational adeno-associated viral vector gene therapy for HA. In the Phase 1/2 program (NCT03003533/NCT03432520), dirloctocogene samoparvovec demonstrated a favourable safety profile and durable Factor (F)VIII expression for up to 6.5 years, with most participants (pts) stabilising within the mild HA range (George, ISTH 2024). PD and PK of dirloctocogene samoparvovec are described.

Methods: Adult males with moderate-severe HA (<2%) and no pre-existing anti-capsid neutralising antibodies received a single dose of dirloctocogene samoparvovec (George, NEJM 2021). Transgene PD measures were FVIII activity assessments [chromogenic substrate assay (CSA) and one-stage assay (OSA)]. PK was assessed as vector shedding in peripheral blood mononuclear cells (PBMCs), saliva, semen, serum and urine.

Results: A total of 25 pts were enrolled across four dose cohorts 15 × 10" (n = 2), 1 × 1012 (n = 3), 2 × 1012 (n = 9), and 1.5 1012 (n = 11) vg/kg]. At data cutoff (8 March 2024), median time since dosing was 4.6 years (range: 1.25-6.5). All pts responded, as evidenced by an initial increase from baseline (BL) FVIII activity after dosing. The median time to peak FVIII activity was 49 days (range: 26-321) across all cohorts. In the two highest dose cohorts, median peak FVIII activity (OSA) was 38.7% (2 × 1012 cohort; range: 7-209) and 55.1% (1.5 × 1012 cohort; 31-112). The two pts in the 5 × 10" cohort had peak FVIII activity (OSA) of 10.8% and 12.1%, and the three in the 1 X 10'2 cohort had peak

activity (OSA) of 6.3%, 20.0% and 24.2%. Transient supraphysiologic FVIII expression (OSA/CSA result >150% was observed in two pts [2 × 1012 cohort; peak FVIII activity (OSA): 194% and 209%]; these levels were not sustained or associated with thrombotic events. The median time to absence of detectable vector was 5.5 weeks (wks; range: 3-12) in PBMCs (n = 22), 2.0 wks (1-2) in saliva (n = 21), 2.0 wks (1-3) in semen (n = 17), 2.0 wks (2-3) in serum (n = 23) and 1.0 wk (1-2) in urine (n = 23).

Discussion/Conclusion: In the cohort who received 1.5 × 10^{12} vg/kg of dirloctocogene samoparvove, median peak FVIII was 55.1% (range: 31%-112%; median 45 days), with no supraphysiologic FVIII activity observed. All pts responded to therapy, as measured by an increase in FVIII activity from BL.

SPK-8011

SPK-8011 vector genome maintains an active transcriptional state for up to 72 weeks in adult mice (PB0877, ISTH 2025)

D. Lupo et al

Background: Clinical studies investigating hemophilia A (HA) gene therapies have utilized diverse capsids, manufacturing techniques, dosing regimens, and DNA sequences. While some HA gene therapies have seen human factor VIII (hFVIII) levels decline over time, SPK-8011 has demonstrated stable FVIII expression in clinic in the mild hemophilia range using a low dose. Previously, a single dose of recombinant adeno-associated virus (rAAV) showed stable hFVIII expression for 72 weeks in C57BL/6 mice.

Aims: To assess the molecular mechanisms driving durability, we evaluated the epigenetic and episomal state of the SPK-8011 vector genome associated with long-term hFVIII expression in a preclinical model.

Methods: An rAAV vector using the identical vector genome to that found in SPK-8011 was intravenously administered at 3.5x1010 vector genomes (vg)/mouse in C57BL/6 mice. Livers were harvested at weeks 5, 24, 48 and 72. Circular vector genome copies were quantified by qPCR to assess episome formation. The epigenetic status of the vector genome was characterized by Assay for Transposase-Accessible Chromatin sequencing (ATAC-seq) and bisulfite sequencing of the promoter on DNA isolated from livers.

Results: Episomal SPK-8011 vector genome was detected up to 72 weeks in murine livers indicating that episomes persist over time. ATAC-seq revealed similar chromatin accessibility of the AAV vector genome at weeks 5 and 72. Bisulfite sequencing found a low mean percentage (week 5: 13.75%; week 72: 13.04%) of methylation in the five CpG sites within the promoter region, and no significant difference (p=0.55, unpaired t-test) between weeks 5 and 72.

Conclusion(s): Our findings demonstrate that stable hFVIII protein expression was associated with episome persistence, accessible chromatin, and a largely unmethylated promoter in mice for 72 weeks (i.e., over half of the lifespan of the model). These results support SPK-8011 as a durable HA therapy.

Etranacogene Dezaparvovec

Completion of phase 2b trial of etranacogene dezaparvovec gene therapy in patients with hemophilia B over 5 years (PubMed 2025)

A. von Drygalski et al

Abstract: Etranacogene dezaparvovec (CSL222, formerly AMT-061) is a recombinant adeno-associated virus serotype 5 (AAV5) vector containing the highly active factor IX (FIX) Padua variant controlled by a liver-specific promoter. This phase 2b, open-label, single-dose, single-arm, multicenter trial evaluated the efficacy and safety of etranacogene dezaparvovec. Three adult participants with severe or moderately severe hemophilia B (FIX ≤2%) and AAV5-neutralizing antibodies received a single IV dose (2 × 1013 genome copies per kg) of etranacogene dezaparvovec. The primary end point of FIX activity ≥5 IU/dL at 6 weeks was met (mean, 30.6 IU/dL). Secondary end points included bleed frequency, FIX concentrate use, and adverse events. Here, we report the end-of-study 5-year outcomes. After administration, mean (range) FIX activity increased to 40.8 IU/dL (31.3-50.2) at year 1 and was maintained at 45.7 IU/dL (39.0-51.2) at year 5. Mean annualized bleeding rate (all bleeds) was 0.14 for the cumulative follow-up period years 0 to 5. Two participants had 5 bleed-free years after treatment. Per protocol, 1 participant received episodic FIX replacement therapy after treatment for elective surgeries, 2 bleeding episodes, and 2 single self-administered infusions for unreported reasons. All participants discontinued and remained free of FIX prophylaxis. During the 5-year study period, there were no clinically significant elevations in liver enzymes, requirement for steroids, FIX inhibitor development, thrombotic complications, or late-emergent safety events in any participant. Five years after administration, etranacogene dezaparvovec was effective in adults with hemophilia B with a favorable safety profile. Participants are eligible to participate in an extension study (ClinicalTrials.gov identifier: NCT05962398) for 10-year additional follow-up. This trial was registered at www.clinicaltrials.gov as #NCT03489291.

Giroctocogene Fitelparvovec

Vector Clearance Following Administration of Giroctocogene Fitelparvovec in Adults With Haemophilia A in the Phase 3 AFFINE Trial (PO044, EAHAD 2025)

H. Alzahrani et al

Introduction: Giroctocogene fitelparvovec is a recombinant adeno-associated virus (AAV) gene therapy for haemophilia A that delivers a B-domain-deleted variant of human Factor VIII (FVIII). An important safety endpoint in AAV gene therapy trials is the time required for viral vector DNA to clear from bodily fluids, avoiding theoretical unintended transmission or long-term effects. We report vector clearance data from the Phase 3 AFFINE trial (NCT04370054).

Methods: Adult men with moderately severe to severe haemophilia A (FVIII<1%) received a single infusion of giroctocogene fitelparvovec 3e13 vg/kg. Vector DNA in plasma, peripheral blood mononuclear cells (PBMCs), semen, saliva and urine was analysed with quantitative real-time

polymerase chain reaction. Measurements were made weekly (every 2 weeks after Week 20) until vector clearance, defined as three consecutive negative results (i.e., below limit of quantification [BLQ]). A proprietary generative AI tool was used with author review to develop the first draft; the authors take full responsibility for the content.

Results: As of June 2024, 75 participants were dosed (median duration of follow-up, 16.8 [range 7.8-44.4] months). Vector DNA was shed in PBMCs, saliva, urine, semen and plasma, with peak levels generally occurring within 2 weeks of infusion. The highest peak vector DNA concentrations were found in plasma (mean 2.76e9 [SD 7.54e9] vg/mL; median 9.85e6 [range 6.32e4-4.54e10] vg/mL) and saliva (mean 1.857 [SD 1.947] vg/mL; median 1.13e 7 [range 3.40e5-1.03e8] vg/mL), whereas the lowest peak level was measured in urine. After reaching the peak, vector DNA concentration declined steadily to BLQ in all matrices. In general, PBMCs were the slowest to clear, with a mean and median time to first of 3 negative results of 219.8 (SD 88.53) and 193.0 (range 120-506) days. In plasma, mean and median time to first of three negative results were 161.5 (SD 85.91) and 145.0 (range 50-491) days; in semen, 56.6 (SD 47.72) and 43.0 (range 16-294) days; in saliva, 45.5 (SD 14.41) and 42.0 (range 30-99) days; and in urine, 19.3 (SD 9.89) and 21.0 (range 1-56) days.

Discussion/Conclusion: Vector DNA declined to levels below the limit of quantification within 3 weeks-5 months post-infusion, except in PBMC, which took ~7.5 months to clear. Full clearance of vector DNA (3 consecutive negative results) was observed in all participants.

Bleed Protection After Giroctocogene Fitelparvovec Infusion in Adults With Moderately Severe to Severe Haemophilia A in the Phase 3 AFFINE Trial (PO045, EAHAD 2025)

M. Ozelo et al

Introduction: Giroctocogene fitelparvovec, a gene therapy designed to increase endogenous Factor VIII (FVIII) expression to prevent or reduce bleeding in individuals with haemophilia A (HA), is evaluated in the ongoing Phase 3 AFFINE (NCT04370054) trial. Superiority in reducing total (treated and untreated) and treated annualised bleeding rates (ABR) versus FVIII prophylaxis was demonstrated post-gene therapy. We describe bleeding events (by cause, by location) and FVIII consumption.

Methods: Adult males with moderately severe to severe HA (FVIII <1%) completed a lead-in study on FVIII prophylaxis before receiving a single 3e13 vg/kg giroctocogene fitelparvovec infusion. Bleeding outcomes are reported in the efficacy population (n = 50) with ≥15-month post-infusion (median follow-up, 33.6 months) and ≥6 months on prophylaxis (median follow-up, 12.5 months). A proprietary generative AI tool was used with author review to develop the first draft; authors take full responsibility for the content.

Results: At June 2024, 75 participants (pts), median age 30 (range 19-59) years, were dosed and 50 pts comprised the efficacy population. Mean total ABR estimates were reduced post gene therapy versus pre-infusion; the highest ABR decrease (treatment difference [95%CI]; 1-sided p value) was for joint bleeds (-2.73 I-4.34, -1.12]; 0.0004). Total ABR estimate reductions for traumatic (-1.34 |-2.28, -0.39]; 0.0027) and protocol-defined target joint (-1.11 [-2.19, -0.02]; 0.0226) bleeds were significant but not for spontaneous (-2.17 [-4.46, 0.12]; 0.0316) and soft tissue (-0.78 [-2.30, 0.75]; 0.1592). Significant reductions in mean (95%CI) treated ABR estimates in post- versus pre-infusion were observed for all bleed types: spontaneous (-2.77 [-3.99, -1.56]; <0.0001), traumatic (-1.23 [-2.13,

-0.33]; 0.0038), all joints (-2.73 |-3.93, -1.52]; <0.0001), soft tissue (-1.35 [-2.17, -0.52]; 0.0007) and target joints (-0.88 [SD: 2.91]; 1-sided p value: 0.0039). Post-infusion, 32 (64%) pts reported zero bleeds. ABR reductions were associated with a 99.8% decrease in mean annualised FVIII consumption post-versus pre-infusion (6.6 vs. 4082.7 IU/kg; treatment difference [95% CI] -4076.1 [-4728.3, -3423.8]; 1-sided p < 0.0001).

Discussion/Conclusion: Giroctocogene fitelparvovec was well tolerated and provided superior bleed protection vs FVIII prophy-laxis, with significant ABR reductions across most bleed causes and locations.

Haemophilia B

Replacement therapies

Protein S aptamer: An adjunct therapy for Hemophilia B (OC 20.2, ISTH 2025)

H. Yu et al

Background: Factor IXa plays a crucial role in coagulation by activating FX which contributes to thrombin generation. Thus, individuals with FIX deficiency are prone to excessive bleeding and hemorrhage in response to even mild injury. The current therapy for HB includes infusion of FIX (plasma-derived or recombinant) and gene therapy. Nonetheless, despite regular intervention, there remains the risk of spontaneous bleeding episodes due to rapid clearing of the infusion from the system. Therefore, an adjunct that extends the functional lifetime of FIX is a necessary enhancement to the current HB therapy.

Aims: Our goal was to identify RNA aptamers against Protein S (PS). By inhibiting the inhibitor of FIXa, we aim to enhance the efficacy of infused FIX, thereby achieving the long-sought goal of a more potent HB replacement therapy.

Methods: RNA aptamers were created using SELEX method with GLA domain proteome selections as starting point and selected with PS. Using Next Generation Sequencing, unique aptamer sequences were obtained which were transcribed in vitro. Binding curves were generated by P32 end-labeling of dephosphorylated RNA with T4 polynucleotide kinase. For functional assays, aPTT, thrombin generation and FXa generation assays were performed and molecular docking predicted interaction sites.

Results: We obtained an aptamer with nM binding affinity and great inhibitory activity against PS. This candidate aptamer interacted with the LG domains of PS, perhaps not allowing interaction with FIXa. Consequently, it inhibited the anticoagulant characteristic of PS as observed by decrease in clotting time and increased thrombin and FX generation.

Conclusion(s): This study suggests that our aptamer might prove to be a very efficient and specific PS inhibitor, with promise of being a candidate for adjunct treatment. We will perform further studies on HB samples to confirm our hypothesis.

Eftrenonacog alfa (Alprolix)

Real-world usage and effectiveness of recombinant factor IX Fc in haemophilia B from the B-SURE study in France (PubMed 2025)

H. Chambost et al

Background: More real-world data are needed to complement existing phase III studies on the efficacy and safety of recombinant factor IX Fc fusion protein (rFIXFc) in people with haemophilia B.

Objectives: We report final data from the B-SURE study, evaluating the real-world usage and effectiveness of rFIXFc in France.

Methods: Previously treated patients (all ages/severities) received on-demand or prophylactic rFIXFc during B-SURE. Annualised bleeding rate (ABR), injection frequency (IF) and factor consumption (FC) were prospectively evaluated for patients on rFIXFc prophylaxis (primary endpoints). Six months of retrospective factor IX (FIX) data were collected for comparison; patients with ⩾3 months of treatment pre- and post-switch to rFIXFc were analysed.

Design: B-SURE was a 24-month, prospective, non-interventional, real-world study across haemophilia treatment centres in France.

Results: Ninety-one male patients enrolled across 21 centres (34% <18 years, 89% severe haemophilia B). Eighty-four patients received prophylaxis at rFIXFc initiation; mean prospective observation period was 21.5 months. Sixty-eight of 84 patients had prior FIX prophylaxis; on rFIXFc prophylaxis, these patients achieved low median ABR (1.2), IF (47.45 injections/year) and mean FC (2844 IU/kg/year). Compared with previous FIX, mean ABR was reduced by 40% (n = 63); mean IF and FC were reduced by 38.20 injections/year and 1008 IU/kg/year (n = 57). In patients with prior FIX on-demand (n = 15), mean ABR reduced by 84% on rFIXFc prophylaxis (n = 14), mean IF reduced by 2.13 injections/year and mean FC increased by 381.8 IU/kg/year (n = 15). Most physicians and patients were satisfied/highly satisfied with rFIXFc prophylaxis. rFIXFc was well tolerated with no new safety concerns.

Conclusion: Findings support the safety and effectiveness of rFIXFc, with reduced IF and FC while maintaining/improving bleed protection.

Real-World Effectiveness and Usage of Recombinant Factor IX Fc: Final Data from the B-MORE Study (PB0868, ISTH 2025)

H. Glosli et al

Background: Extended half-life (EHL) recombinant factor IX Fc fusion protein (rFIXFc) has an established efficacy and safety profile in people with hemophilia B across all ages.

Aims: Here, we report final data from B-MORE (NCT03901755), a real-world, 24-month prospective study evaluating rFIXFc effectiveness and usage across Europe and the Middle East.

Methods: Eligible patients, including previously untreated patients, were prescribed rFIXFc prophylaxis (PPX) or on-demand prior to/at enrolment. Twelve-month retrospective data on previous FIX (as available), baseline characteristics, and follow-up on rFIXFc (retrospective/prospective periods) are reported. Annualized endpoints only include patients with ≥6 months treatment.

Methods: Eligible patients, including previously untreated patients, were prescribed rFIXFc prophylaxis (PPX) or on-demand prior to/at enrolment. Twelve-month retrospective data on previous FIX (as available), baseline characteristics, and follow-up on rFIXFc (retrospective/prospective periods) are reported. Annualized endpoints only include patients with ≥6 months treatment.

Results: B-MORE enrolled 151 patients from 29 centers (median [range] age: 20.5 [1-81] years; three patients were female). Twelve patients were previously untreated; 119 had severe hemophilia (26 moderate, 6 mild). For the primary endpoints, 137 patients prospectively treated with rFIXFc PPX were analyzed (mean [range] treatment duration: 22.4 [7.3-30.0] months). Median (interquartile range [IQR]) annualized bleeding rate (ABR) was 0.45 (0.0-1.2), annualized injection frequency (IF) was 52.5 (52.2-52.6), and annualized factor consumption (FC) was 2,442.7 (2,021.9-2,969.7) IU/kg/year. An intrapatient comparison was conducted in 92 patients switching from prior standard half-life (SHL) FIX PPX to rFIXFc PPX (mean [range] duration: 11.5 [6.4-12.0] vs 40.6 [9.8-83.3] months). In these patients, median (IQR) change in ABR was 0.0 (-1.0-0.4) change in IF was -52.7 (-56.6- -38.4), and change in FC was -1,379.9 (-2,594.4- -264.3; n=91) IU/kg/year. Overall, most physicians (88.5%; 69/78) and patients (90.0%; 90/100) were satisfied/highly satisfied with rFIXFc PPX, at last assessment. No inhibitor development or serious adverse events related to rFIXFc were reported.

Conclusion(s): Real-world B-MORE data confirm the effectiveness of rFIXFc and demonstrate that rFIXFc PPX can reduce IF and FC while improving/maintaining bleed protection, compared with SHL PPX.

Efmoroctocog alfa (Elocta)

Real-World Effectiveness and Usage of a Recombinant Factor VIII Fc: Interim Analysis in Adults from the 48-Month Prospective, Observational A-MORE Study (PO120, EAHAD 2025)

O. B. Hidalgo et al

Introduction: Improvement in joint health has been observed in persons with haemophilia A (PwHA) undergoing extended half-life (EHL) efmoroctocog alfa (herein termed rFVIIIFc) prophylaxis (PPX). However, continued real-world evidence is needed to further corroborate this finding. Here, we report results from the 4th interim analysis on the adult population enrolled in the ongoing A-MORE study.

Methods: The 48-month prospective, non-interventional A-MORE study (NCT04293523) is evaluating joint health outcomes in PHA of all ages/severities receiving rFVIIIFc PPX across 14 countries in Europe/the Middle East. This descriptive analysis presents data from the adult (≥18 years old at enrolment) population with recorded follow-up, including a 12-month retrospective period.

Results: At data cutoff (8 July 2024), 232 PwHA (of which one female) with median age of 35.0 (range: 18-83) were enroled. Median (range) observational period was 29.8 (0-47.2) months. Mean prescribed dose (SD) during this period was 80 (29) IU/kg/week, with a median [interquartile range (IQR)] weekly injection frequency of 2.0 (2.0-3.0). Model-based mean [95% confidence interval (CI)] annualised bleed rates (ABRs) and joint ABRs (AjBRs) were low at baseline (1.04 (0.79-1.39) and 0.66 (0.47-0.94), respectively] and remained low throughout the observational period [0.70 (0.56-0.88) and 0.49 (0.38-0.63), respectively]. Percentages of PwHA experiencing zero bleeds in the prior 12 months were 63.8% (N = 148/232) at baseline, then 63.8% (N = 143/224), 65.9% (N = 135/205) and 74.8% (N = 104/139) at 12, 24 and 36 months, respectively. Mean [standard error (SE)] total Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scores remained relatively

stable, from 12.5 (1.3) at baseline to a least-square estimated 11.1 (1.2) at 36 months, as determined via a mixed model repeated measures based on patients with at least 1 assessment (n = 83). Similarly, total Haemophilia Joint Health Score (HJHS) remained stable (n = 87), from baseline mean (SE) of 19.9 (2.4) to 20.4 (2.5).

Discussion/Conclusion: A-MORE Interim 4 data show that PPX with rFVIIIFc offers long-term effective bleed and joint protection in adults with haemophilia A, aligning with previous analyses.

Real-World Effectiveness and Usage of a Recombinant Factor VIII Fc: Interim Analysis in Children and Adolescents from the 48-Month Prospective, Observational A-MORE Study (PO079, EAHAD 2025)

M. Olivieri et al

Introduction: Continued real-world evidence is warranted to confirm the observed long-term improvement in joint health associated with extended half-life (EHL) efmoroctocog alfa (herein termed rFVIIIFc) prophylaxis (PPX) in persons with haemophilia A (PHA). Here, we present results from the 4th interim analysis on the paediatric and adolescent population enrolled in the A-MORE study.

Methods: A-MORE (NCT04293523) is an ongoing 48-month prospective, non-interventional study evaluating joint health in PwHA of all ages/severities receiving rFVIIIFc PPX across 14 countries in Europe/the Middle East. This descriptive analysis presents outcomes in children and adolescents (<18 years at enrolment) with recorded follow-up, including a 12-month retrospective period.

Results: At data cutoff (8 July 2024), 187 children and adolescents with haemophilia A with median age of 8.3 (range: 0-17) were enroled. Median (range) observational period was 26.9 (0-42.6) months. Mean prescribed dose (SD) during this period was 97 (50) IU/kg/week, with a median [interquartile range (IQR)] weekly injection frequency of 2.0 (2.0-2.5). Model-based mean [95% confidence interval (CI)] annualised bleed rates (ABRs) and joint ABRs (AjBRs) were low at baseline [0.74 (0.56-0.98) and 0.31 (0.20-0.47), respectively] and remained low by the end of the observational period [0.55 (0.42-0.71) and 0.26 (0.19-0.36), respectively]. Percentages of children and adolescents experiencing zero bleeds in the prior 12 months were 62.0% (N = 116/187) at baseline, then 70.3% (N = 128/182), 69.8% (N = 118/169) and 64.8% (N = 59/91) at 12, 24 and 36 months, respectively. Mean [standard error (SE)] total Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scores were low at baseline [1.2 (0.3)] and remained so [least-square estimated: 1.5 (0.5)] at 36 months, as determined via a mixed model repeated measures based on patients with at least 1 assessment (n = 59). Stable total Haemophilia Joint Health Scores (HJHS) were also observed with an equivalent model (n = 90), showing baseline mean (SE) of 1.2 (0.3) to 1.6 (0.4).

Discussion/Conclusion: 4th interim data from A-MORE show that PPX with rFVIIIFc offers effective bleed and joint protection in children and adolescents with haemophilia A, thus aligning with previous analyses on the overall population.

Gene Therapy

Sustained Clinical Benefit of AAV Gene Therapy in Severe Hemophilia B (The New England Journal of Medicine, 2025)

U. M. Reiss et al

Background: Adeno-associated virus (AAV)–mediated gene therapy has emerged as a promising treatment for hemophilia B. Data on safety and durability from 13 years of follow-up in a cohort of patients who had been successfully treated with scAAV2/8-LP1-hFIXco gene therapy are now available.

Methods: Ten men with severe hemophilia B received a single intravenous infusion of the scAAV2/8-LP1-hFIXco vector in one of three dose groups (low-dose: 2×1011 vector genomes [vg] per kilogram of body weight [in two participants]; intermediate-dose: 6×1011 vg per kilogram [in two]; or high-dose: 2×1012 vg per kilogram [in six]). Efficacy outcomes included factor IX activity, the annualized bleeding rate, and factor IX concentrate use. Safety assessments included clinical events, liver function, and imaging.

Results: Participants were followed for a median of 13.0 years (range, 11.1 to 13.8). Factor IX activity remained stable across the dose cohorts, with mean factor IX levels of 1.7 IU per deciliter in the low-dose group, 2.3 IU per deciliter in the intermediate-dose group, and 4.8 IU per deciliter in the high-dose group. Seven of the 10 participants did not receive prophylaxis. The median annualized bleeding rate decreased from 14.0 episodes (interquartile range, 12.0 to 21.5) to 1.5 episodes (interquartile range, 0.7 to 2.2), which represented a reduction by a factor of 9.7. Use of factor IX concentrate decreased by a factor of 12.4 (interquartile range, 2.2 to 27.1). A total of 15 vector-related adverse events occurred, primarily transient elevations in aminotransferase levels. Factor IX inhibitor, thrombosis, or chronic liver injury did not develop in any participant. Two cancers were identified but were deemed by the investigators, together with an expert multidisciplinary team, as being unrelated to the vector. A liver biopsy that was conducted in 1 participant 10 years after the infusion revealed transcriptionally active transgene expression in hepatocytes without fibrosis or dysplasia. Levels of neutralizing antibodies to AAV8 remained high throughout follow-up, thus indicating potential barriers to readministration of the vector.

Conclusions: A single administration of scAAV2/8-LP1-hFIXco gene therapy resulted in durable factor IX expression, sustained clinical benefit, and no late-onset safety concerns over a period of 13 years. These data support the long-term efficacy and safety of AAV gene therapy for severe hemophilia B.

CSL220 (formely AMT-060)

AMT-060, etranacogene dezaparvovec in haemophilia B: duration of freedom from bleeding & prophylaxis (PB0780, ISTH 2025)

A. von Drygalski et al

Background: The durability of transgene-derived Factor IX (FIX) expression and its haemostatic effect remain as questions in the field of haemophilia B (HB) gene therapy. AMT-060 (expressing wild-type F9 gene) is the precursor of etranacogenedezaparvove (formerly AMT-061; expressing Padua variant F9), which utilize the same capsid and the same gene expression cassette having only a 2-nucleotide difference in the F9 cDNA.

Aims: Here, we report the durability defined by sustained FIX activity levels and haemostatic protection of AMT-060 and etranacogenedezaparvove in severe or moderately severe HB.

Methods: Data from 3 clinical trials in adults with severe or moderately severe HB have been captured: phase 1/2 study (AMT-060; N=5; NCT02396342; 8 years); phase 2b study of etranacogenedezaparvovec (N=3; NCT03489291; 5 years); phase 3 HOPE-B study of etranacogenedezaparvovec (N=54; NCT03569891; 4 years). Informed consent was obtained. Studies were approved by medical ethics committees of the participating institutions.

Results: Of 62 participants treated with 2x1013 gc/kg AMT-060 or etranacogenedezaparvovec, 60 expressed transgene-derived FIX/FIX Padua; and 2 did not express FIX Padua in HOPE-B (high AAV5 NAb titer of 1:3212, n=1; received 10% of the planned dose, n=1). Endogenous mean FIX activity levels remained stable in all studies (Table). The proportion of participants free from bleeds ranged from 60-80% per year up to 4- and 5-years post-etranacogenedezaparvove and up to 8-years post-AMT-060 (Table). All (100%) participants from phase 1/2 and phase 2b studies remained free of continuous FIX concentrate prophylaxis up to their respective data cut (8- and 5- years post-treatment); all studies combined 59/60 (98%) remained free of continuous prophylaxis during the current follow-up.

Conclusion(s): HB gene therapy with AMT-060 and etranacogenedezaparvove has maintained durable effectiveness and is stable for the duration of the individual follow up periods of the trials.

Etranacogene dezaparvovec (Hemgenix)

Four-year results of etranacogene dezaparvovec in haemophilia B patients without AAV5 neutralising antibodies: Phase 3 HOPE-B trial (PO040, EAHAD 2025)

P. Raheja et al

Introduction: In contrast to most adeno-associated virus (AAV)-based gene therapy clinical trials, the phase 3 HOPE-B trial (NCT03569891) demonstrated the superiority of etranacogene dezaparvovec (CSL222, HEMGENIX®) over continuous factor IX (FIX) prophylaxis both in patients with and without pre-existing neutralising antibodies (NAbs). Long-term data on HOPE-B subjects

without NAbs (NAb-) are necessary for accurate indirect comparison to other haemophilia B (HB) gene therapy trials. This analysis aimed to evaluate long-term efficacy and safety of etranacogene dezaparvovec from the HOPE-B trial over 4 years in NAb- subjects.

Methods: 54 adult male subjects with severe or moderately severe HB (FIX ≤2%) received a single infusion of etranacogene dezaparvovec after a ≥ 6-month lead-in period on their regular continuous FIX prophylaxis. Of these, 33 were NAb-. Efficacy and safety endpoints in this NAb- group are reported over 4 years post-treatment.

Results: All 33 NAb- subjects (mean age 39.5 years at consent) completed 4-year follow-up. Mean ABR (all bleeds) reduced by 85%, from 3.80 during the lead-in period to 0.57 during Months 7–48 post-treatment ($p<0.0001$). FIX-treated bleeds made up 81.6% of total bleeds during lead-in and 37.2% post-treatment. Mean ABR for spontaneous bleeds reduced by 89% from 1.04 during lead-in to 0.12 during Months 7–48 post-treatment ($p<0.0001$). All 33 NAb- subjects expressed FIX Padua; mean (SD) endogenous FIX activity levels were 40.6 IU/dL (18.6, n=33) at Month 6 and stable at 39.0 IU/dL (16.83, n=33) at Year 4 post-treatment. No subjects returned to continuous FIX prophylaxis. FIX consumption decreased by 99% over 4 years post-treatment compared with the lead-in period ($p<0.0001$). All subjects experienced at least one treatment-emergent adverse event (AE) in the 4 years post-treatment. Of the 455 reported events, 78% were mild, 19% moderate and 3% severe. There were no treatment-related serious AEs, inhibitor development or thrombotic events. The most frequent AE was an elevation in alanine transaminase, with 6/33 (18.2%) of subjects receiving corticosteroid treatment.

Conclusion: The HOPE-B trial shows etranacogene dezaparvovec provides long-term 4-year stable FIX activity levels in the near-normal range and bleed protection in all treated NAb- subjects, with a favourable safety profile.

Four-year results of etranacogene dezaparvovec in haemophilia B patients with pre-existing AAV5 neutralising antibodies: Phase 3 HOPE-B trial (PO037, EAHAD 2025)

R. Klamroth et al

Introduction: The phase 3 HOPE-B trial (NCT03569891), studying the effect of a single-dose of etranacogene dezaparvovec (CSL222, HEMGENIX®) in individuals with haemophilia B (HB), included subjects with pre-existing AAV5 neutralising antibodies (NAb+); unique for haemophilia adeno-associated virus (AAV)-gene therapy trials. Herein, previously unreported 4-year outcomes in NAb+ subjects are shown.

Methods: 54 adult male subjects with severe or moderately severe HB (factor IX [FIX] ≤2%) received etranacogene dezaparvovec after a ≥6-month lead-in period on FIX prophylaxis. Efficacy and safety endpoints in the NAb+ group are reported at 4 years post-treatment.

Results: Of 21 NAb+ subjects (mean age 44.5 years at consent), 20 completed safety (death, n=1) and 18 completed efficacy (consent withdrawal for efficacy data, n=1; liver transplant, n=1) 4-year follow-up. Median (IQR) NAb titer was 56.9 (23.3–198.9); 20 subjects had titer ≤678. All but two subjects (high NAb titer 3212, n=1; received ~10% dose, n=1) expressed FIX Padua. Unadjusted annualized bleeding rate (ABR) (all bleeds) dropped 75%, from 4.64 in lead-in to 1.18 (n=21) during Months 7–48. ABR for spontaneous bleeds reduced from 2.17 to 0.46 in Months 7–18, with all

subjects free of spontaneous bleeds in Year 4. Mean endogenous FIX activity levels were 35.9% (n=18) at Month 6 and stable at 33.7% (n=14) at Year 4. One patient returned to prophylaxis in Year 3 (previously reported), no subject returned to prophylaxis in Year 4. FIX consumption was reduced by 90% during Year 4 compared with the lead-in period ($p<0.0001$; n=21). A total of 339 adverse events (AEs; 69% mild, 25% moderate, 6% severe) were reported in 21 subjects during 4 years post-treatment. There was no inhibitor development or thrombotic events. Serious AEs unrelated to treatment were previously reported (HCC, n=1; death, n=1). During Year 4, glossopharyngeal schwannoma (n=1) and myelodysplastic syndrome (n=1) have been explored with molecular analysis (unrelated to treatment, and ongoing, respectively). The most frequent AE was alanine transaminase elevation; 3 (14.3%) subjects received corticosteroid treatment.

Conclusion: Etranacogene dezaparvovec is the only gene therapy providing adults with pre-existing Nabs long-term ≥4-year stable FIX activity levels in the mild/normal range and bleed protection, with a favourable safety profile.

The phase 3 HOPE-B trial shows 4-year durability of sustained near-normal FIX activity, bleed protection and favourable safety in adults with severe or moderately severe haemophilia B

F. W. G. Leebeek et al

Introduction: Etranacogene dezaparvovec (CSL222, HEMGENIX®) is the first and only approved gene therapy for haemophilia B (HB) worldwide in patients with and without pre-existing neutralising antibodies (NAbs). The HOPE-B pivotal phase 3 clinical trial (NCT03569891) demonstrated superior bleed protection of etranacogene dezaparvovec (an adeno-associated virus serotype 5 [AAV5] vector containing factor IX [FIX] Padua transgene) compared with FIX prophylaxis up to 3 years post-treatment and long-term durability is still being studied.

Methods: 54 adult male subjects with severe or moderately severe HB, with (n=21) or without (n=33) pre-existing AAV5 NAbs, received etranacogene dezaparvovec following a ≥6-month lead-in period of their usual FIX prophylaxis. Efficacy and secondary endpoints at 4 years post-treatment for all subjects dosed are reported.

Results: 53 subjects completed safety (death, n=1 [already reported, unrelated to treatment]) and 51 completed efficacy (consent withdrawal for efficacy data, n=1; liver transplant [month 28], n=1) follow-up to 4 years post-treatment. Mean endogenous FIX activity was stable and sustained at 41.5 IU/dL (n=50), 36.7 IU/dL (n=50), 38.6 IU/dL (n=48) and 37.4 (n=47) at Years 1, 2, 3 and 4, respectively. Mean annualised bleeding rate (ABR) for all bleeds reduced vs lead-in (4.16) to 1.33, 0.91, 0.83 and 0.40 at Year 1 (n=54), Year 2 (n=54), Year 3 (n=53) and Year 4 (n=51), respectively. Mean ABR for joint bleeds reduced from 2.35, to 0.43, 0.29, 0.33 and 0.09. Two subjects had no FIX expression, one returned to continuous FIX prophylaxis during Year 3 (all previously reported), and no subject resumed prophylaxis during Year 4. Mean annualised FIX consumption during Year 4 was reduced by 96% vs lead-in ($p<0.0001$). A total of 98 treatment- related adverse events (AEs), five during Year 4, were reported in 39/54 (72%) subjects, with no treatment-related serious AEs (SAEs). During Year 4, two SAEs of glossopharyngeal schwannoma and myelodysplastic syndrome have been explored with molecular analysis (unrelated to treatment, and ongoing, respectively).

Conclusion: The HOPE-B trial confirms etranacogene dezaparvovec provides long-term 4-year stable FIX activity levels in the mild/normal range and bleed protection, with a favourable safety profile.

Natural History of AAVS Neutralising Antibodies in Adults With Haemophilia B During ≥6-Month Screening and Lead-In to the HOPE-B Trial with curanacogene Dezaparvovec Gene Therapy (PO025, EAHAD 2025)

R. Klamroth et al

Introduction: Testing for neutralising antibodies (NAbs) to adeno-associated virus serotype 5 (AAV5) is part of the laboratory assessment of people with haemophilia B (HB) considering treatment with etranacogene dezaparvovec (CSL222) gene therapy. We evaluated the natural historv of NAn titres during the lead-in period of the Phase 3 HOPE-B trial (NCT03489291) prior to infusion of etranacogene dezaparvove to thoroughly characterise changes in Nabs over time.

Methods: Adult males ≥18 years old with HB (Factor IX ≤2%) enrolled in the Phase 3 trial entered a ≥6-month lead-in period in which they received their usual Factor IX prophylaxis. Blood was collected at screening, then at 1-2-month intervals over a period of >6 months. A AV5 antibodies (Abs) were measured with a trans duction inhibition assay for NAbs (precision ≤30%; reportable range: 7-8748) and indirect ELISAs for immunoglobulin (Ig) G-or IgM-binding Abs (precision ≤30%; 50-109,350).

Results: At screening, 48% (32/67) of enrolled patients had detectable NAbs (NAb+) with a median titre of 58 (range: 9-3440). The median duration of the patient NAb data collection period was 240 days (range: 1-360). The median intra-patient coefficient of variation of NAb titres over time was 25% (range 2%-154%) and patient NAb titres remained stable during the lead-in relative to screening values. NAb seropositivity was associated with older age (p - 00069) For patients with detectable anti-AAVS NAbs and total IgG, there was a high correlation of titres at each visit (median r = 0.94; range: 0.28-0.99). IgM Abs were usually undetectable. One patient clearly seroconverted to NAb+, with NAb and IgM undetectable at screening and 4 months later titres were 82 and 139, respectively; another converted to NAb+ after 8 months without IgM Abs being detected.

Discussion/Conclusion: AAV5 NAbs were stable over >6 months. NAbs were consistently highly correlated with IgG anti-AAVS Abs. These data can help inform patient-management decisions for etranacogene dezaparvovec.

Etranacogene dezaparvovec in haemophilia B: a 48-month post hoc responder analysis of HOPE-B (OC 69.4, ISTH 2025)

S. W. Pipe et al

Aims: We report a 4-year follow-up of HOPE-B participants expressing factor IX (FIX).

Background: Etranacogene dezaparvovec is the first gene therapy approved for haemophilia B, based on interim analyses from the HOPE-B trial (NCT03569891).

Conclusion(s): Single-dose etranacogene dezaparvovec provides durable FIX-Padua expression, sustained ABR reduction, and a significant decrease in FIX consumption over 4 years. Etranacogene dezaparvovec remained well tolerated, with no new safety signals.

Methods: HOPE-B is a single-arm study of adult males with haemophilia B (FIX ≤2%). The ethics committee approved HOPE-B; consents were obtained. Fifty-four participants, with/without pre-existing adeno-associated virus (AAV5) neutralizing antibodies, received a single dose of etranacogene dezaparvovec after a 6-month lead-in period on their regular, continuous FIX prophylaxis. Of these, 52 expressed transgene-derived-FIX and discontinued prophylaxis. Post-hoc analyses of main efficacy outcomes and safety in responders are reported. FIX activity is reported as the mean (standard deviation [SD]; min-max).

Results: At 4 years, FIX activity remained stable: 39.0 IU/dL (±18.7; 8.2-97.1) at Month 6, 36.7 IU/dL (±19.0; 4.7-99.2) at Year 2, 38.6 IU/dL (±17.8; 4.8-80.3) at Year 3, 37.4 IU/dL (±16.7; 4.7-80.1) at Year 4. Mean annualized bleeding rate (ABR; all bleeds) decreased from 4.00 (lead-in) to 0.40 (Year 4), a 90% reduction ($p<0.0001$). ABR for bleed subtypes was also markedly reduced. Participants with zero bleeds increased from 25.0% during lead-in to 59.6%, 63.5%, 74.5%, and 72.0% at Years 1, 2, 3, 4, respectively. Mean (SD) FIX consumption decreased from 262,077 (±149,818) IU/year (lead-in) to 5419.5 (±18,565) IU/year (Months 7-48); 98.1% of responders remained FIX prophylaxis-free during follow-up. No genotoxicity due to AAV integration or late hepatotoxicity was observed, including in participants with transient early transaminase increases or prior chronic viral hepatitis.

Long-term safety and efficacy of etranacogene dezaparvovec in hemophilia B (IX-TEND-3003 study) (PB0843, ISTH 2025)

S. Gill et al

Background: The haemophilia community wants to understand durability, hepatotoxicity and potential risk of genotoxicity of adeno-associated virus (AAV)-based gene therapies for haemophilia. Etranacogenedezaparvovec (CSL222), an AAV type 5 vector delivering the highly active factor IX (FIX) Padua transgene, has demonstrated durable significant reductions in bleeding and stable FIX activity levels in the near-normal range, with no liver damage or AAV-related genotoxicity, over 5 years posttreatment in a phase 2b trial (NCT03489291) and over 4 years post-treatment in the phase 3 HOPE-B trial (NCT03569891).

Aims: Longer-term follow-up of gene therapy is a post-marketing requirement and is needed to substantiate the long-term safety and efficacy of gene therapy for haemophilia.

Methods: Participants who completed the phase 2b and phase 3 trials may enrol in the international IX-TEND 3003 extension study (NCT05962398) assessing the long-term safety and efficacy of etranacogenedezaparvovec previously administered to adult males with haemophilia B.

Results: After providing consent, participants will be monitored for long-term safety and efficacy until 15 years posttreatment with etranacogenedezaparvovec in either parent trial. Participants will visit the clinic every 6 months (Years 5 to 10 post-treatment) and then annually (Years 11 to 15 posttreatment). The duration of the IX-TEND 3003 study for each participant is 10 years. Currently, up to 55 participants of the parent trials are eligible for enrolment. Primary and secondary endpoints are summarized in Tables 1 and 2. The protocol was approved by all applicable competent health

authorities and Institutional Review Boards. First interim analysis is planned 3 years after initial participant enrolment. The first participant was enrolled on the 30th of August 2023. Study design, timelines and enrollment status will be presented.

Conclusion(s): This study will provide long-term safety and efficacy data from adult males with haemophilia B treated with etranacogenedezaparvovec in a clinical trial setting

BBM-H901

Gene transfer with BBM-H901: results of long term follow up in Chinese Hemophilia B (OC 69.2, ISTH 2025)

F. Xue et al

Background: BBM-H901 is a novel vector composed of liver-trophic AAV843 and a cassette expressing a hyperactive Padua factor IX (FIX) protein. In 2019 we started a single-center, single-arm, pilot trial evaluating the safety and efficacy of a single intravenous infusion of BBM-H901 in 10 Chinese hemophilia B patients. The study was approved by ethics committees of Blood diseases hospital, CAMS. NCT04135300.

Aims: To present long-term safety, FIX coagulation activity (FIX:C) and bleeding events for patients treated with BBM-H901.

Methods: Ten hemophilia B patients (FIX≤2% and aged≥18) were successfully enrolled and dosed with a single infusion of BBM-H901(5E12 vg/kg) from October 2019 to January 2021. The main follow up period was 52 weeks after BBM-H901 infusion. And the long follow up period is 52 weeks -5 years after infusion. The endpoint includes AE/SAE. FIX:C, bleeding event etc.

Results: Nine patients were follow-up for a median 186 weeks (Range 181 to 243 weeks). At all patients' latest follow-up, the mean(‡SD) FIX:C level was 48.38(22.10)% measured by one stage APTT based method using Dade Actin FSL(Siemens, Germany) reagents. The mean FIX:C level at each time point maintains stable expression after BBM-H901 treatment (Figure). One patient had dropped out after 159 weeks of BBM-H901 infusion. The latest FIX level was 2.0%. There were no deaths, SAEs associated with BBM-H901, thrombotic events, or FIX inhibitors. All the nine participants had no bleeding events and replacement therapy in a long follow up period.

Conclusion(s): This study suggests that BBM-H901 is safe more than 3.5 years after infusion. Vector derived FIX:C level is sufficiently high to prevent bleeding events and minimize the need for replacement therapy in HB patients.

ETX-148

Efficacy and Safety of ETX-148 in Murine Models of Haemophilia A and B (OR10, EAHAD 2025)

N. Pursell et al

Introduction: People with haemophilia (PwH) continue to be plagued by recurrent haemarthroses, or joint bleeds. Despite recent approvals, a high unmet need remains for safe and effective prophylactic treatments with a lower treatment burden to improve quality of life. e-Therapeutics used its HepNet computational platform to identify protein Z-dependent protease inhibitor (ZPI) as a novel liver-expressed target gene involved in haemostasis. Inhibition of ZPI in plasma from PwH has recently been shown to increase thrombin generation, further supporting ZPI as a therapeutic target for the treatment of bleeding disorders. Potent siRNAs targeting ZPI were designed in silico and tested in vivo to select the lead GalOmic siRNA, ETX-148, which is being developed for the treatment of rare bleeding disorders, including haemophilia.

Methods: Pharmacodynamic activity of top-ranked siRNAs was measured in non-human primates (NHPs). To establish the disease-modifying potential of ETX-148 in haemophilia, a mouse-active ETX-148 surrogate siRNA (mETX-148) was tested in mouse models of haemophilia A (HA) and haemophilia B (HB). mETX-148 was first tested in a mouse model of severe haemarthrosis where haemophilia mice were pre-treated with mETX-148 and subjected to injury of a single knee joint. Mice were then monitored for 10 days for evidence of bleeding before terminal histopathological analysis. To demonstrate compatibility of prophylactic ETX-148 treatment with emergency treatments, mETX-148 was further tested in haemophilia mice alone or in combination with on-demand therapies to assess thrombosis risk. Lastly, high-dose mETX-148 was chronically administered to C57BL/6 mice to demonstrate the safety of sustained ZPI knockdown.

Results: ETX-148 demonstrated deep and sustained knockdown of ZPI mRNA and protein in NHPs, supporting a quarterly dosing regimen in PwH. Treatment of HA and HB mice with mETX-148 resulted in significant improvement in joint pathology in the hemarthrosis model. Administration of mETX-148 was well-tolerated alone and in combination with emergency treatments, with no evidence of increased thrombosis risk.

Discussion/Conclusion: Despite recent advances in the treatment of haemophilia, high unmet need remains. These results highlight the potential of ETX-148 as a safe and effective prophylactic treatment for haemophilia with a patient-friendly quarterly, subcutaneous dosing regimen.

Bypassing Agents

Real-World Effectiveness of Eptacog Beta in the USA (PO104, EAHAD 2025)

R. F. Sidonio, Jr. et al

Introduction: In the United States, eptacog beta is indicated for the treatment of bleeding events (BEs) in adults and adolescents with haemophilia A or B with inhibitors (HABI). There is limited data on eptacog beta (SEVENFACT) use in real-world practice.

Methods: This retrospective study was performed at 8 U.S. sites on data collected retrospectively from medical charts, bleeding diaries and medication logs. The primary objective was to describe the effectiveness of eptacog beta using the Clinical Global Impression-Efficacy (CGI-E) Index. Response to treatment was categorised as 'efficient', 'minimally efficient', 'inefficient' or 'not assessable. All adverse drug events during eptacog beta exposure were recorded.

Results: Sixteen males (including 4 children <12years old) with HABI (N = 15) or FXIII deficiency (N = 1) received eptacog beta for the treatment of BEs (bleeding events), prevention of bleeding during surgery or invasive procedures or prophylaxis. Thirteen patients received concomitant treatment with emicizumab prophylaxis. Eptacog beta was used to treat 113 BEs in 14 patients, of which 105 were assessed by CGI-E (103 as 'efficient', 1 'minimally efficient' and 1 'inefficient'). As 90 BEs were reported in a single adult patient with all BEs rated as 'efficient', a sensitivity analysis excluding this patient was performed. For the remaining patients, 8 had 15 assessable BEs rated as 'efficient' (n = 13), 'minimally efficient' (n = 1) and 'inefficient' (n = 1). Among the three children with assessable BEs the overall CGI-E rating was 'efficient' for two children (3 BEs) and 'minimally efficient' for one child (1 BE). Overall, the median time to bleed control was 2 h. Eptacog beta was used for 10 surgical procedures (seven minor, two major and one unknown) in six patients; six events in four patients were assessable and all were rated 'efficient' for postoperative bleed control. Three children had five assessable surgeries/procedures (including one major); all CGI-E ratings were 'efficient. One adult received ongoing eptacog beta prophylaxis due to a high annualised bleeding rate, however without CGI-E data available. No adverse events related to study drug (thromboembolic events, immune or allergic responses) were reported.

Discussion/Conclusion: In this real-world study, eptacog beta treatment was effective and safe in persons with HABI.

Re-balancing Therapies

Concizumab (brand name Alhemo)

Annualized bleeding rates in hemophilia A/B and target joints: Concizumab explorer8 study (OC 59.2, ISTH 2025)

A. Wheeler et at

Background: In severe hemophilia, prophylaxis is the current standard-of-care, started early in life to prevent joint damage and progression to hemophilic arthropathy. Concizumab is an anti-tissue factor pathway inhibitor monoclonal antibody intended for hemophilia A/B (HA/HB) with/without inhibitors, approved in the US for once-daily, subcutaneous prophylaxis in HA/HB with inhibitors.

Aims: Assess annualized bleeding rate (ABR) during concizumab prophylaxis vs on-demand treatment in HA/HB with or without target joints at baseline in the prospective, multicenter, open-label, phase 3 explorer8 study (NCT04082429).

Methods: Patients were randomized 1:2 to on-demand (arm 1) or concizumab (arm 2), or assigned to non-randomized concizumab arms 3/4. Patients received a 1.0 mg/kg concizumab loading dose (Day 1), followed by 0.20 mg/kg daily starting from Day 2+, with potential dose adjustment (5-8 weeks) to 0.15 or 0.25 mg/kg based on concizumab plasma concentration measured after week 4. Informed consent/ethics committee approval were obtained. Target joints were defined as ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period. Treated spontaneous/traumatic bleeding episodes were assessed at 32- and 56-week cut-offs.

Results: Of the 96 (HA) and 77 (HB) male patients ($12 years) screened, 21 were randomized to on-demand (arm 1), 42 to concizumab (arm 2), and 85 allocated to concizumab (arms 3/4). At the 32-week cut-off, there was a 77% and 99% reduction in treated spontaneous and traumatic bleeding episodes with concizumab (arm 2) vs on-demand (arm 1) in patients with and without target joints, respectively. Median ABRs [interquartile range] for treated spontaneous and traumatic bleeding episodes during concizumab prophylaxis (arms 2-4) were low at 32 weeks for patients with (2.9 [0.4-6.4]) and without (1.6 [0.0-4.5]) target joints, remaining low at 56 weeks.

Conclusion(s): In explorer8, once-daily, subcutaneous concizumab prophylaxis effectively reduced ABR vs on-demand, independent of target joint presence at baseline.

Marstacimab

Long-Term Efficacy of Marstacimab in Participants With Severe Hemophilia A or B Without Inhibitors (OC 20.1, ISTH 2025)

P. Sun et al

Background: Marstacimab targets tissue factor pathway inhibitor (TFPI) to improve hemostasis. NCT05145127 is an open-label extension (OLE) of the phase 3 BASIS trial (NCT03938792). The BASIS trial demonstrated efficacy and safety of marstacimab for reducing bleeding episodes in participants aged 12 to <75 yr with severe hemophilia A (HA) or B (HB) without inhibitors compared with previous on-demand and routine prophylaxis factor therapy.

Aims: To describe the long-term efficacy of marstacimab in adults and adolescents with severe HA or HB without inhibitors who completed the BASIS trial and OLE.

Methods: Eligible participants were male, aged 12 to <75 yr with severe HA or HB without inhibitors who completed the BASIS trial. Participants entered the OLE on their marstacimab dose from the end of the BASIS study (150 or 300 mg QW). Bleeds and marstacimab doses were captured by electronic diary. We describe long-term efficacy.

Results: In total, 107/116 (92.2%) of the non-inhibitor participants from the BASIS trial enrolled and were dosed in the OLE: 89 (83%) adults and 18 (17%) adolescents. Participants in the OLE had a median exposure of 18.9 months (range 1.2-29.4) with a combined median exposure (BASIS+OLE) of 30 months (range 0.9-41.5). Across BASIS and OLE, 27 (23.3%) participants had dose escalated from 150 to 300 mg QW. Annualized bleeding rate (ABR) for treated and total bleeds are shown in Tables 1 and 2, respectively. Marstacimab remains generally safe and well tolerated. Deep vein thrombosis was reported (non-life-threatening and without hospitalization) in one participant in the OLE. Intervention included anticoagulant and the participant is doing well. Participant had multiple risk factors, including heterozygous factor V Leiden mutation, lifestyle risks, and family history of acute coronary syndrome.

Conclusion(s): Long-term data from the longest reported follow-up use of an anti-TFPI in participants with HA or HB without inhibitors supports sustained efficacy of marstacimab as demonstrated by maintenance of reduced bleeding and a trend of decreasing ABR over time for treated and total bleeds. The overall benefit-risk profile of marstacimab remains favorable.

Marstacimab Prophylaxis in Hemophilia A/B Without Inhibitors: Results from the Phase 3 BASIS Trial (Blood 2025)

D. Matino et al

Background: Marstacimab is a monoclonal antibody that targets the tissue factor pathway inhibitor to rebalance hemostasis. Previous phase 1 and 2 trials established marstacimab safety and efficacy in adults with severe hemophilia A or B. BASIS is an open-label, phase 3 trial of marstacimab in males aged 12–74 years with severe hemophilia A (factor VIII <1%) or moderately severe to severe hemophilia B (factor IX ≤2%). Participants without inhibitors received on-demand (OD) or routine prophylaxis (RP) factor replacement during a 6-month observational phase (OP) before receiving

once-weekly subcutaneous 150 mg marstacimab prophylaxis during a 12-month active treatment phase (ATP). Primary endpoints were annualized bleeding rate (ABR) for treated bleeds vs prior OD or RP during the OP and safety. Of 128 participants enrolled in the OP, 116 received marstacimab in the ATP. In the OD group (n=33), mean ABR (95% CI) decreased from 39.86 (33.05-48.07) in the OP to 3.20 (2.10-4.88) in the ATP, demonstrating superiority of marstacimab (estimated ABR ratio, 0.080 [0.057-0.113]; P < .0001). In the RP group (n=83), mean ABR decreased from 7.90 (5.14-10.66) in the OP to 5.09 (3.40-6.78) in the ATP, demonstrating noninferiority and superiority of marstacimab (estimated ABR difference, –2.81 [–5.42 to –0.20]; P = .0349). There were no deaths or thromboembolic events. Weekly subcutaneous marstacimab reduced ABR compared with OD or RP therapy in the OP in individuals with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors. Marstacimab was safe and well tolerated with no unanticipated side effects. This trial was registered at www.clinicaltrials.gov as # NCT03938792.

Von Willebrand Disease and Other Rare Bleeding Disorders

Bleed experience in von Willebrand disease and validation of a Bleed and Medication Questionnaire (PB1383, ISTH 2025)

J. Mahlangu et al

Background: Type 3 von Willebrand disease (VWD) is an ultra-rare disorder, characterized by a virtual absence of von Willebrand factor (James et al., 2021). Validated tools to assess site, impact, and management of bleeding in VWD are limited. We developed a Bleed and Medication Questionnaire-VWD (BMQ-VWD) to assess bleeding in people with VWD.

Aims: To assess the content validity of the BMQ-VWD to assess bleeding in people with VWD and their caregivers' experience.

Methods: This was a non-interventional, cross-sectional qualitative interview study approved by ethics committees and sponsored by Roche/Genentech. Participants were US-based adults (aged ≥18 years) and adolescents (aged 12-17 years) with Type 3 VWD, plus caregivers of children (aged 2-11 years) with Type 3 VWD; all provided informed consent. The BMQ-VWD was developed and assessed through one-time 75-minute semi-structured interviews conducted in two segments: concept elicitation of bleed experiences and management, and cognitive debriefing of the BMQ-VWD.

Results: Twenty-three participants, comprising 10 adults (5 women; 5 men), 7 adolescents (5 women; 2 men), and 6 caregivers (of 1 girl, 3 boys, and 2 undisclosed gender), were interviewed. Most (n=18) had Type 3 VWD; due to its rarity, people with Type 1 or 2 VWD and their caregivers were also recruited (n=5). Modifications to the BMQ-VWD were made after the first wave of interviews (n=9) and tested in the second wave (n=14). Nose and mouth bleeds were most common. Bleeds at all locations impacted participants' physical wellbeing. Bleeds were managed with prophylaxis, on-demand treatment, and technical (e.g., rest, ice, compression, elevation, pressure) and/or coping (e.g., activity avoidance) strategies.

Conclusion(s): This study provides evidence that the BMQ-VWD is relevant to people with Type 3 VWD (including adolescents) and caregivers of children with VWD, and appropriately captures their bleed experience/management. Overall, it indicates that the BMQ-VWD is content valid in the target population.

VELORA Pioneer: first-in-human safety and PK/PD study of HMB-002 in Type 1 Von Willebrand disease (LB 01.4, ISTH 2025)

P. Rahera et al

Background: Von Willebrand disease (VWD) results from quantitative or qualitative defects in von Willebrand factor (vWF), essential for both primary (platelet adhesion) and secondary (factor VIII stabilization) hemostasis. vWF deficiency results in recurrent hemorrhagic events across severity

levels, with episodes requiring appropriate therapeutic management including intravenous replacement therapy with vWF/FVIII. HMB-002 is a monovalent antibody that aims to offer convenient subcutaneous prophylaxis by binding to and elevating levels of endogenous circulating vWF and thereby also increasing FVIII.

Aims: Here, we present interim results from the first-in-human study of HMB-002 in VWD.

Methods: VELORA Pioneer (NCT06754852) is a first-in-human, phase 1/2, open-label study evaluating HMB-002 in adults with Type 1 VWD (baseline vWF activity ≤40 IU/dL). Participants in Cohort A1 (n = 3) received a single 20mg subcutaneous dose of HMB-002. Part A aims to evaluate safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects.

Results: Following a single subcutaneous dose of HMB-002 in A1 cohort, all participants showed substantial increases in endogenous circulating vWF with consistent PK profiles. Mean baseline vWF antigen was 23.6 IU/dL (23.0 - 23.9 IU/dL). Within 14 days, mean vWF rose to 38.1 IU/dL (29.7 - 45.6 IU/dL), a >1.5-fold increase with vWF levels anticipated to be above baseline for 29 days. FVIII levels were concurrently elevated by > 1.5-fold, increasing from 43.7 IU/dL to 67.4 IU/dL. Pharmacokinetic modeling estimated HMB-002 half-life of 35.9 days. No injection-site reactions, hypersensitivity, or serious adverse events were reported.

Conclusion(s): This first-in-human study demonstrates HMB-002, even at lowest planned dose, induces robust and sustained increases in vWF and FVIII levels in Type 1 VWD. Pharmacokinetic profile supports infrequent subcutaneous dosing. These data validate HMB-002's novel mechanism and potential as a subcutaneous prophylaxis addressing VWD's root cause rather than episodic replacement. VELORA Pioneer is ongoing with additional cohorts to further evaluate dosing, safety, and efficacy in preventing bleeding events with HMB-002.

Phase I Study of VGA039, a Protein S-Targeting Monoclonal Antibody, in Individuals With von Willebrand Disease Demonstrates Sustained Drug Concentrations, Increased Thrombin Generation and Decreased Bleeding Following a Single Subcutaneous Injection (PO239, EAHAD 2025)

A. Chiavarella et al

Introduction: Non-factor replacement therapies can provide haemostatic balance in various bleeding disorders with less frequent dosing than factor concentrate prophylaxis. Preclinical studies of VGA039 have demonstrated its ability to increase thrombin generation across multiple inherited bleeding dis-orders, including von Willebrand disease (VWD). In healthy volunteers (HVs), single ascending doses (SADs) of subcutaneous (SC) VGA039 increase thrombin generation in a dose- and concentration-dependent manner.The objective of this SAD study is to investigate the safety, toler-ability, pharmacokinetics and pharmacodynamics of SC VGA039 in VWD patients.

Methods: This is an open-label phase I study (NCT05776069) conducted in adult individuals with VWD. Key eligibility criteria included: (1) symptomatic VWD of any type or subtype, (2) baseline FVIII activity level ≤50 IU/dL and (3) no laboratory evidence of thrombophilia or prior history of thromboembolism. Dose escalations were determined based on emerging D-dimer levels, with a dose-limiting toxicity (DLT) threshold set at four times the upper limit of normal (2.0 ug/mL).

Results: As of 23 October 2024, a total of seven subjects have been dosed with 3.0 or 4.5 mg/kg of SC VGA039: 1 with Type 1 VWD + mild haemophilia A, 1 with Type 2A VWD, 2 with Type 2M VWD and 3 with Type 3 VWD. There were no drug-related adverse events, changes in coagulation laboratory parameters, thromboembolic events, DLTs or injection-site reactions reported to date. VGA039 concentrations predicted to increase thrombin generation in VWD subjects to levels measured in HVs at baseline were sustained for >4 weeks following a single, SC 4.5 mg/kg dose. Two evaluable 4.5 mg/kg subjects with historical annualised bleeding rates (ABRs) >50 had reductions of 75% and 88% after a single dose of VGA039; the third evaluable subject had only 1 bleed post-VGA039. Efficacy for additional 4.5 mg/kg subjects will become evaluable in time for presentation at the meeting.

Discussion/Conclusion: VGA039 was safe and well tolerated in this SC SAD study in VWD subjects across all types. ABR reductions at VGA039 concentrations associated with increased thrombin generation, in the absence of DLTs, have been observed. SC multi-dose VGA039 investigation is planned.

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	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	Pfizer (originally 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)	Approved by EMA in July 2024, brand name Durveqtix, also approved by FDA and Health Canada as Beqvez
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 1
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	Pre-clinical phase

					Innovators' Open Technology Programme, Project#18712	

CELL BASED THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	Haemophilia A with inhibitors	TI-168	Autologous FVIII TCR-Treg cell therapy	-	TeraImmune Inc.	Phase 1/2a clinical trial planned for 2024, Orphan drug status granted by FDA
Cell-based therapy	Haemophilia B	BE-101	Engineered B Cell medicine	Single infusion	Be Biopharma	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	-	Grifolds	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	Haemophilia A	Octanate	-	Octapharma	Licensed
Replacement FVIII	Haemophilia A	Emoclot/Klott/Emowil	-	Kedrion	Licensed
Replacement FVIII	Haemophilia A	Beriate	-	CSL Behring	Licensed
Replacement FVIII	Haemophilia A	Immunate	-	Takeda	Licensed
Replacement FVIII	Haemophilia A	Factane	-	LFB	Licensed
Replacement FVIII	Haemophilia A	Haemoctin	-	Biotest	Licensed
Replacement FVIII	Haemophilia A	Koate DVI	-	Grifolds	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
Replacement Fibrinogen	Fibrinogen disorders	CLOTTAFACT	-	LFB	Licensed
Replacement Fibrinogen	Fibrinogen disorders	RiaSTAP	-	CSL Behring	Licensed
Replacement Fibrinogen	Fibrinogen disorders	Fibryga	-	Octapharma	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Uman Complex D.I.	-	Kedrion	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Confidex	-	CSL Behring	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Beriplex	-	CSL Behring	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Octaplex	-	Octapharma	Licensed
Replacement Factor II (Prothrombin)	Factor II (Prothrombin) Deficiency	Cofact	-	Prothya Biosolutions	Licensed

LICENSED BYPASSING AGENTS					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	Haemophilia A or B w/ inhibitors	Sevenfact®/ Cevenfacta®	Recombinant FVIIa- jncw	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	Roche	Licenced

LICENSED NON-FACTOR 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

EHC

Empowering the bleeding disorders community