EHC
Empowering the bleeding disorders community

Novel treatments in haemophilia and other bleeding disorders

A periodic EHC Review

January 2025 - Issue

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Foreword

Welcome to the first 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 EHC New Technologies Workshop held in November 2024 and the American Society of Hematology (ASH) Annual Meeting held in December 2024, 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 July 1, 2024.

The second section, Report Highlights, summarises very concisely some of the key advances since the last edition of this review in July 2024 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/13652516/2024/30/S1
WFH abstracts: https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14973
ISTH abstracts: https://isth2024.eventscribe.net/index.asp?launcher=1
ASH abstracts: https://ash.confex.com/ash/2024/webprogram/start.html

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
- Dr Ana Boban, EHC volunteer
- Dr Mariette Driessens, EHC volunteer
- Dr Radoslaw Kaczmarek, EHC volunteer
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- Prof Johannes Oldenburg, 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 concentrates*	**IV**	*Intravenous*
CHMP	*Committee for Human Medicinal Products*	**MAD**	*Multiple-ascending dose*
CI	*Cumulative Incidence*	**nAb**	*Neutralizing antibody*
CI	*Confidence Intervals*	**OD**	*On demand*
CID	*Clinically important differences*	**OSA**	*One stage assay*
CL	*Clearance*	**PK**	*Pharmacokinetics / 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 analysis*	**SD**	*Standard deviation*
DNA	*Deoxyribonucleic acid*	**TFPI**	*Tissue factor pathway inhibitor*
DMC	*Data Monitoring Committee*	**VWD**	*Von Willebrand disease*

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

Factor Replacement Therapies

Efanesoctocog alfa (brand name Altuvoct in Europe and Altuviiio in the U.S.), an ultra-extended half-life FVIII for the treatment of haemophilia A, manufactured by Sanofi/Sobi, received marketing authorisation from the European Commission in June 2024. It is indicated for the treatment and prevention of bleeds and perioperative prophylaxis for all ages is available for compassionate use throughout the European Union.

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

Star Therapeutics' investigational monoclonal antibody, VGA039, has gained fast track designation from the US Food and Drug Administration (FDA) for the treatment of von Willebrand disease (VWD).

Phase 3 clinical trial results for Mim8, a next-generation bispecific antibody that mimics the role of FVIII in the coagulation cascade, were released and the manufacturer, Novo Nordisk, has announced it will make the first submissions for marketing authorisations later in early 2025..

Rebalancing therapies

Following approvals in Canada, Australia and Japan in 2023 for the treatment of adolescents (12 years and older) and adults with haemophilia A and B with inhibitors requiring prophylaxis, Concizumab (brand name Alhemo), an anti-tissue-factor pathway inhibitor (TFPI), received EU marketing authorisation.

European Commission (EC) has granted marketing authorisation for marstacimab (brand name Hympavzi), intended for prophylaxis of bleeding episodes in patients aged 12 years and older, weighing at least 35 kg, who have severe haemophilia A or B.

The U.S. Food and Drug Administration (FDA) is reviewing a submission to approve fitusiran, a subcutaneous, prophylactic small interfering (siRNA) therapeutic, as a treatment for adults and adolescents with haemophilia A and B with or without inhibitors. according to fitusiran's developer, Sanofi. A decision is expected by end of March 2025.

Centessa Pharmaceuticals is discontinuing the clinical development of SerpinPC, its experimental subcutaneous therapy for people with hemophilia A and hemophilia B with or without inhibitors. This follows Centessa's decision to prioritize capital toward the development of its OX2R agonist program and after being evaluated in several Phase 2 clinical trials.

Gene therapy for haemophilia A

Biomarin Pharmaceutical announced that it is limiting commercial development of hemophilia A gene therapy Roctavian (valoctocogene roxaparvovec-rvox) to only the U.S., Germany, and Italy.

Metagenomi, which is developing MGX-001, a gene-editing therapy for haemophilia A, is preparing to initiate investigational new drug (IND)-enabling activities that seek to support the therapy's transition from preclinical to clinical testing. The move is backed by preclinical studies in nonhuman primates that show the treatment led to a sustained increase in the activity of factor VIII (FVIII), the missing clotting protein in hemophilia A, over a year.

Sangamo Therapeutics regains development and commercialization rights to giroctocogene fitelparvovec, an investigational gene therapy product candidate for the treatment of adults with moderately severe to severe haemophilia A., following a decision by Pfizer to terminate the global collaboration and license agreement between the parties.

Spark Therapeutics / Roche announced the discontinuation of dirloctocogene samoparvovec (SPK 8011, adeno-associated viral vector with B-domain deleted human FVIII gene) in adults with severe or moderately severe haemophilia A.

Results from a small single-center study on Gene Therapy with CD34+ Hematopoietic Cells for Hemophilia A by A. Srivastava and et showed that treatment with a gene therapy involving the use of lentiviral vector-transduced autologous hematopoietic stem cells (HSCs) increased factor VIII levels in patients with severe hemophilia A. Among five patients, the median factor VIII activity level from 4 weeks until the last follow-up visit increased to 5.2 and 1.7 IU/dL with a peripheral-blood vector copy number of 0.2 and 0.1 copies/cell, respectively, in the two participants in group 1 (who did not receive a transduction enhancer), and 37.1, 19.3, and 39.9 IU/dL with a peripheral-blood vector copy number of 4.4, 3.2, and 4.8 copies/cell, respectively, in the three participants in group 2 (who received a transduction enhancer).

Gene therapy for haemophilia B

Fidanacogene elaparvovec (brand name Durveqtix in Europe and Beqvez in North America) gene therapy for haemophilia B was given conditional marketing authorisation by the EMA in July 2024. Durveqtix is indicated for the treatment of severe and moderately severe haemophilia B in adult patients without a history of FIX inhibitors and without detectable antibodies to variant AAV serotype Rh74. Beqvez was approved by the U.S. FDA in April 2024 and by Health Canada in December 2023. In January 2024, Canada's Drug Agency (previously CADTH) issued a positive reimbursement recommendation, conditional on a price reduction.

A Phase 3 study has shown that the gene therapy fidanacogene elaparvovec significantly reduces bleeding in adults with hemophilia B, decreasing the annualized bleeding rate by 71% and maintaining factor IX activity levels at 26.9% (on average but with marked variability) 15 months after treatment. Fidanacogene elaparvovec was superior to prophylaxis for the treatment of participants with hemophilia B, leading to reduced bleeding and stable factor IX expression.

Regeneron has begun the first-in-human trial testing a CRISPR/Cas9-based Factor 9 (F9) gene-insertion therapy for people with haemophilia B. The announcement of the planned launch of the Phase 1 clinical trial follows the recent approval by the U.S. Food and Drug Administration (FDA) of an investigational new drug (IND) application.

In an oral abstract presented at ASH 2024, the update was provided on the first-in-human Phase 1/2 clinical trial testing BE-101, Be Biopharma's B-cell treatment candidate for hemophilia B, is now enrolling patients at two sites in the U.S. BE-101, a first-in-class therapy, aims to address the persistent unmet needs of hemophilia B patients — particularly the burden of ongoing treatment and disease management for the "many people living with hemophilia B. The two-part Phase 1/2 trial — dubbed BeCoMe-9 (NCT06611436) — was designed to assess the safety and clinical activity of a single intravenous, or into-the-vein, infusion of BE-101 in adults with moderately severe to severe hemophilia B.

Transcutaneous auricular nerve stimulation

In a poster presented at ASH 2024, Spark Biomedical gave an update on the phase 1 clinical trial recruiting 10 women with Type 1 VWD to test transcutaneous auricular nerve stimulation. A wearable device sends signals from the ear along the vagal nerve to the spleen to improve clotting at the site of bleeding. Vagus nerve stimulation targets acetylcholine-producing T lymphocytes in the spleen and α7 nicotinic acetylcholine receptors (α7nAChR) on platelets to increase calcium uptake and enhance alpha granule release.

Section 2 - Report highlights

An update on novel therapies in haemophilia A

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

Mim8

Safety and Efficacy of Mim8 Prophylaxis Administered Once Every Two Weeks for Patients with Hemophilia A with or without Inhibitors: Interim Analysis of the FRONTIER4 Open-Label Extension Study

In the oral presentation at ASH 2024, Tadashi Matsushita et al reported the interim analysis of the FRONTIER4 Open-Label Extension Study. It demonstrated that Mim8 Q2W prophylaxis was well tolerated, with no patients discontinuing treatment through 26 weeks of FRONTIER4. Few patients experienced treated bleeding episodes with Mim8 Q2W dosing, and 84% had zero treated bleeding episodes. These findings are consistent with those using QW and QM prophylaxis in the pivotal study, supporting the use of different maintenance dosing frequencies with Mim8 for patients with hemophilia A with or without inhibitors.

Mim8 Prophylaxis Beyond Bleeding: Investigating Multifaceted, Patient-reported Outcomes for Hemophilia A in the FRONTIER2 Study

In the abstract at ASH 2024, Cedric Hermans et al reported patient-reported outcomes for Haemophilia A in the FRONTIER2 Study. Hemo-TEM results indicated that treatment burden was reduced with Mim8 prophylaxis after 26 weeks, and patients completing the Hemophilia Patient Preference Questionnaire (HPPQ) expressed a strong preference over on-demand treatment and their previous CFC prophylaxis. JPRS scores did not change notably over the 26 weeks, with patients in all arms except the on-demand arm reporting low baseline pain intensity. However, most patients experienced an individual reduction in pain intensity (as assessed by the PGI questionnaire). These findings highlight the holistic benefits of Mim8 prophylaxis beyond bleed protection and provide insights into opportunities for individualized care.

Factor Replacement Therapies

Efanesoctocog alfa (brand name **Altuvoct)**

Long-term outcomes with efanesoctocog alfa prophylaxis for previously treated children with severe haemophilia A, an interim analysis of the phase 3 XTEND-ed study

Lynn Malek et al published the XTEND-ed study, a rollover from the XTEND-Kids study, evaluating long-term data on safety and efficacy of **efanesoctocog alfa (Altuvoct)** in previously treated children with severe haemophilia A. The study found that no FVIII inhibitors were detected. The mean ABR was 0.70, thus maintaining the low mean ABR observed in the parent study (0.88). Most bleeds (86%; 30/35) resolved with a single dose of efanesoctocog alfa 50 IU/kg, with 96% (23/24) of

hemostatic responses rated as excellent or good. They concluded that The results from over 2 years in previously treated children with severe hemophilia A show that once-weekly efanesoctocog alfa continues to be well tolerated and provides highly effective bleed protection with no FVIII inhibitors reported.

Pre-clinical evaluation of an enhanced-function factor VIII variant for durable hemophilia A gene therapy in male mice

Overall, 43 (61%) participants experienced ≥1 treatment-emergent adverse event (TEAE) and 2 (3%) experienced ≥1 serious TEAE. They concluded that long-term results in children with severe haemophilia A in XTEND-ed show that once-weekly efanesoctocog alfa continues to be well tolerated, with no FVIII inhibitors reported, and provides highly effective bleed protection.

Gene Therapy

Valoctocogene roxaparvovec (brand name **Roctavian)**

Efficacy and safety of valoctocogene roxaparvovec 4 years after gene transfer in GENEr8-1

Leavitt et al published the phase 3 efficacy and safety outcomes 4 years post-**valoctocogene roxaparvovec** treatment. During year 4, 81/110 (73.6%) participants had 0 treated bleeds and 68/110 (61.8%) participants had 0 bleeds regardless of treatment. At week 208, mean CSA and OSA FVIII activity was 16.1 and 27.1 IU/dL. During year 4, the most common adverse event was alanine aminotransferase (ALT) elevation (56/131 participants; ALT >upper limit of normal or ≥1.5x baseline); no participants initiated immunosuppressants for ALT elevation. They concluded that Valoctocogene roxaparvovec provides persistent FVIII expression, hemostatic control, and health-related quality of life improvements with no new safety signals.

An update on novel therapies in haemophilia B

Gene Therapy

CSL220 (formely AMT-060)

Stable factor IX expression and sustained reductions in factor IX use 8 years after gene therapy with AMT-060 in adults with haemophilia B

In the poster at ASH 2024, W. Miesbach presented that Phase I/II extension study (NCT05360706) will follow patients through 15 years post-AMT-060 administration for long-term efficacy (e.g., joint health, QoL) and safety assessments. This 8-year follow-up after AMT-060 administration confirms the safety, durability and stability of FIX expression after AAV-based gene therapy reported previously.

An Update on Rebalancing Therapies

Concizumab

In an oral communication at ASH 2024, A. Shapiro et al presented results from the Concizumab Phase 3 Explorer7 Study. In the explorer7 study, once-daily, subcutaneous concizumab prophylaxis effectively reduced ABR irrespective of the presence of target joints at baseline at the 32-week cut-off, and low ABRs were maintained at the 56-week cut-off.

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

VGA039

In a poster at ASH 2024, C. M. Millar et al presented results for **VGA039** from a Phase 1a trial in healthy volunteers. VGA-039 is a Protein S-targeting monoclonal antibody. Preclinical studies of VGA039 have demonstrated its ability to increase thrombin generation across multiple inherited bleeding disorders, including von Willebrand disease (VWD). 30 healthy volunteers in 4 IV and 2 SC SAD cohorts have been dosed. No adverse events related to VGA039, including thromboembolic events, DLTs, or infusion-related/injection-site reactions, have occurred. At higher tested doses, VGA039 increased ex vivo thrombin generation compared to baseline. Researchers concluded that well tolerated and can increase thrombin generation in the absence of clinically significant D-dimer elevations in individuals with VWD. Drug concentration data continue to support the potential for weekly or less frequent SC prophylactic dosing. Further SAD evaluation of VGA039 in VWD patients is ongoing, and future multi-dose and surgical prophylaxis investigation is planned.

Section 3 - research abstracts and articles

Haemophilia A

Bispecific Monoclonal Antibodies Mimetics (including FVIII Mimetics)

Emicizumab (Hemlibra)

Emicizumab prophylaxis in infants with haemophilia A (HAVEN 7): primary analysis of a phase 3b open-label trial (ASH 2024)

Steven Pipe et al

Subcutaneous emicizumab enables prophylaxis for people with haemophilia A (HA) from birth, potentially reducing risk of bleeding and intracranial hemorrhage (ICH). HAVEN 7 (NCT04431726) is the first clinical trial of emicizumab dedicated to infants, designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in those aged ≤12 months with severe HA without factor VIII (FVIII) inhibitors. Participants in this phase 3b trial received emicizumab 3 mg/kg maintenance dose every 2 weeks for 52 weeks and are continuing emicizumab during the 7-year long-term follow-up. Efficacy end points included annualized bleed rate (ABR): treated, all, treated spontaneous, and treated joint bleeds. Safety end points included adverse events (AEs), thromboembolic events (TEs), thrombotic microangiopathies (TMAs), and immunogenicity (anti-emicizumab antibodies [ADAs] and FVIII inhibitors). At primary analysis, 55 male participants had received emicizumab (median treatment duration: 100.3; range, 52-118 weeks). Median age at informed consent was 4.0 months (range, 9 days to 11 months 30 days). Model-based ABR for treated bleeds was 0.4 (95% confidence interval, 0.30–0.63), with 54.5% of participants (n = 30) having zero treated bleeds. No ICH occurred. All 42 treated bleeds in 25 participants (45.5%) were traumatic. Nine participants (16.4%) had ≥1 emicizumab-related AE (all grade 1 injection-site reactions). No AE led to treatment changes. No deaths, TEs, or TMAs occurred. No participant tested positive for ADAs. Two participants were confirmed positive for FVIII inhibitors. This primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors.

Factor Replacement Therapies

Efanesoctocog alfa (Altuvoct, Altuviiio)

Efanesoctocog Alfa Prophylaxis for Children with Severe Hemophilia A (N Engl)

L. Malec et al.

Background: Once-weekly efanesoctocog alfa provides high sustained factor VIII activity with superior bleeding prevention as compared with prestudy factor VIII prophylaxis in previously treated

patients 12 years of age or older with severe hemophilia A. Data on outcomes of efanesoctocog alfa treatment in children younger than 12 years of age with severe hemophilia A are limited.

Methods: We conducted a phase 3, open-label study involving previously treated patients younger than 12 years of age with severe hemophilia A. Patients received prophylaxis with once-weekly efanesoctocog alfa (50 IU per kilogram of body weight) for 52 weeks. The primary end point was the occurrence of factor VIII inhibitors (neutralizing antibodies against factor VIII). Secondary end points included annualized rates of treated bleeding episodes, bleeding treatment, safety, and pharmacokinetics.

Results: A total of 74 male patients were enrolled (38 with an age of <6 years and 36 with an age of 6 to <12 years). No factor VIII inhibitors developed. Most adverse events were nonserious. No serious adverse events that were assessed by the investigator as being related to efanesoctocog alfa were reported. In the 73 patients treated according to the protocol, the median and model-based mean annualized bleeding rates were 0.00 (interquartile range, 0.00 to 1.02) and 0.61 (95% confidence interval, 0.42 to 0.90), respectively. A total of 47 patients (64%) had no treated bleeding episodes, 65 (88%) had no spontaneous bleeding episodes, and 61 (82%) had no episodes of bleeding into joints. A total of 41 of 43 bleeding episodes (95%) resolved with one injection of efanesoctocog alfa. Mean factor VIII activity at steady state was more than 40 IU per deciliter for 3 days and more than 10 IU per deciliter for almost 7 days after dose administration. The geometric mean terminal half-life was 40.0 hours.

Conclusions: In children with severe hemophilia A, once-weekly prophylaxis with efanesoctocog alfa provided high sustained factor VIII activity in the normal to near-normal range (>40 IU per deciliter) for 3 days and more than 10 IU per deciliter for almost 7 days after administration, leading to effective bleeding prevention. Efanesoctocog alfa was associated with mainly nonserious adverse events. (Funded by Sanofi and Sobi; XTEND-Kids ClinicalTrials.gov number, NCT04759131.)

Patient Experience With Efanesoctocog Alfa for Severe Hemophilia A: Results From the XTEND-1 Phase 3 Clinical Study Exit Interviews (PubMed 2024)

D. DiBenedetti et al

Purpose: Hemophilia A is a rare bleeding disorder that leads to recurrent hemarthrosis, which can ultimately result in reduced mobility and poor quality of life. Qualitative exit interviews provide insights into patient perspectives and support the interpretation of quantitative trial data, such as patient-reported outcome measures. In the Phase 3 XTEND-1 study (NCT04161495) of efanesoctocog alfa in participants with severe hemophilia A, exit interviews were conducted to understand pre- and post-study experiences with pain and physical functioning and to evaluate participants' treatment experiences.

Methods: In XTEND-1, participants (≥12 years old) received once-weekly efanesoctocog alfa prophylaxis 50 IU/kg for 52 weeks (Arm A) or on-demand efanesoctocog alfa 50 IU/kg for 26 weeks followed by 26 weeks once-weekly prophylaxis (50 IU/kg; Arm B). Optional qualitative exit interviews were conducted using a semi-structured guide in a subset of participants following study completion. Interviews included open-ended questions about participants' pre- and post-study experiences with hemophilia A and targeted questions relating to improvements in patient-reported outcomes assessed during XTEND-1, including the Haemophilia Quality of Life Questionnaire for

Adults Physical Health subscale (Haem-A-QoL PH). Content validity of the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a measure was also assessed, particularly the worst pain item.

Findings: Exit interviews were conducted with 29 of 159 patients enrolled in XTEND-1 (mean [range] age 40 [16–73] years). Of 17 participants enrolled in Arm A, 13 (76.5%) reported a "wearing off" feeling with pre-study treatment, including more aches/pain, breakthrough bleeds, and limited physical activities. Joint pain was the most reported pre-study symptom (96.6%; n = 28/29), followed by a reduced ability to move without pain (89.7%, n = 26/29). Improvements following efanesoctocog alfa prophylaxis in ≥1 Haem-A-QoL PH domain were reported by 89.7% (n = 26/29) of participants, with improvements in joint pain, the ability to move without pain, and painful swellings reported by at least 21 (84%) participants. Participants reported that the PROMIS Pain Intensity 3a items were relevant, clear, and easy to answer. Most participants (96.6%) were "quite satisfied" or "very satisfied" with efanesoctocog alfa prophylaxis. All participants preferred efanesoctocog alfa over pre-study treatment.

Implications: The exit interviews demonstrated that once-weekly efanesoctocog alfa prophylaxis resulted in patient-relevant and meaningful improvements in pain and physical functioning, consistent with the quantitative findings from XTEND-1. These results support the validity of the Haem-A-QoL PH and PROMIS Pain Intensity 3a assessed during XTEND-1, demonstrating the potential for change with efficacious treatment.

Association between Hemophilia Joint Health Score and Quality of Life Using Results from the Xtend-1 Efanesoctocog Alfa Phase 3 Trial (ASH 2024)

C. Königs et al

Introduction: In people with hemophilia A, repeated bleeding may result in joint deterioration leading to joint replacement, chronic pain, impaired physical functioning, and reduced health-related quality of life (QoL). Effective prevention of bleeding has been shown to prevent joint deterioration in people with hemophilia A. In the Phase 3 XTEND-1 study (NCT04161495) in patients assigned to receive weekly prophylaxis with efanesoctocog alfa, joint health improved from baseline to Week 52. Significant improvements were also seen at Week 52 in the Haem-A-QoL Physical Health (PH) score and the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity worst score.

Aim: Using data from the XTEND-1 study, this post-hoc analysis investigated the association, at baseline and after 1 year of efanesoctocog alfa treatment, between joint health (measured by Hemophilia Joint Health Scores [HJHS]) and patient-reported outcomes (PROs) across the following domains: pain, physical functioning, and overall QoL.

Methods: Patients included in the XTEND-1 study were previously treated adults and adolescents aged ≥12 years with severe hemophilia A without inhibitors. This analysis included patients on prior standard-of-care prophylaxis factor VIII who received once-weekly prophylactic efanesoctocog alfa for 52 weeks during the study. Joint health was measured by HJHS total score (ranging from 0 to 124, with higher scores indicating worse joint health); endpoints were baseline score and change from baseline (CFB) at Week 52. HJHS CFB at Week 52 was categorized into two subgroups ("Maintenance" [-2< CFB <2] or "improvement" [CFB ≤-2] versus "Worsening" [CFB ≥2]). PRO

domains were Pain Intensity (PROMIS Pain Intensity worst score, ranging from 1 [no pain] to 5 [very severe pain], and T-score, ranging from 30.7 to 71.8), overall QoL (Haem-A-QoL total score, ranging from 0 to 100), and Physical Function (Haem-A-QoL PH score and PROMIS Physical Function [PF] T-score, ranging from 21.0 to 59.0). Lower scores represent lower pain and better physical health; except for PROMIS PF, where higher values represent better physical function. Spearman correlations between HJHS total scores and PRO scores were computed at baseline. The least-squares (LS) means CFB in PRO scores at Week 52 were estimated and compared between HJHS subgroups using analysis of covariance models, with HJHS subgroups, age, baseline HJHS total score, and baseline PRO scores as covariates. All p-values are nominal.

Results: Of the 133 patients in XTEND-1 receiving efanesoctocog alfa prophylactically, 116 patients had a HJHS total score at baseline; of these, 107 also had a change from baseline score at Week 52. At baseline, HJHS total score was strongly correlated (absolute correlations) to Physical Function (Haem-A-QoL PH [0.65] and PROMIS PF T-score [-0.71]), moderately correlated to Haem-A- QoL total score (0.51), and weakly to moderately correlated to Pain Intensity worst score (0.34) and T-score (0.43). "Worsening" and "Maintenance or improvement" HJHS subgroups included 14% and 86% of patients at Week 52, respectively. A greater and significant improvement in QoL PROs was observed in patients with a maintenance or improvement in HJHS subgroup compared with patients who worsened in HJHS. LS mean difference (95% confidence interval) between QoL PROs CFB at Week 52 in "Maintenance or improvement" and "Worsening" HJHS subgroups were: PROMIS Pain Intensity worst score -0.61 (-1.17 to -0.05; p=0.032), PROMIS Pain Intensity T-score -3.79 (-7.56 to -0.02; p=0.049), Haem-A-QoL total score -6.21 (-12.38 to -0.05; p=0.048), Haem-A-QoL PH score -2.65 (-4.63 to -0.67; p=0.009), and PROMIS PF T-score 3.34 (5.99 to 0.69; p=0.014).

Conclusions: Our findings indicate a stronger improvement in PROs across the three domains of pain, physical functioning, and overall QoL, in patients with joint improvement or maintenance compared with patients with joint worsening, thus highlighting the importance of improved or preserved joint health in patients with hemophilia A. Prospective validation is warranted to confirm these data.

Clinical Outcomes over 3 Years of Once-Weekly Efanesoctocog Alfa Treatment in Adults and Adolescents with Severe Hemophilia A: Second Interim Analysis from the Phase 3 XTEND-ed Long-Term Extension Study (ASH 2024)

R. Klamroth et al

Introduction: Efanesoctocog alfa (formerly BIVV001) is a first-in-class high-sustained 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. Here we present data from the second interim analysis of the long-term safety and efficacy of efanesoctocog alfa in adults and adolescents with severe hemophilia A in the XTEND-ed study (NCT04644575).

Methods: Previously treated patients (≥12 years) who completed XTEND-1 could continue efanesoctocog alfa (50 IU/kg, once-weekly) prophylaxis in the multicenter, open-label, long-term XTEND-ed study (Arm A). The primary endpoint is incidence of FVIII inhibitor development (determined by the Nijmegen modified Bethesda assay). Secondary endpoints include annualized

bleed rates (ABRs), efficacy for bleed treatment, patient-reported quality of life (QoL) outcomes, and safety. XTEND-ed was approved by local ethics committees; participants provided informed consent. Data cut: February 22, 2024.

Results: A total of 146 participants (including 1 female) rolled over from XTEND-1 to Arm A of XTEND-ed (age: 12–17 years, n=21; 18–64 years, n=120; ≥65 years, n=5). The median (range) treatment duration in XTEND-ed was 120.6 (14.1–140.6) weeks comprising a median (range) of 121.5 (14–147) exposure days (EDs). The median (range) cumulative treatment duration from XTEND-1 baseline was 170.5 (46.3–192.6) weeks with median (range) 171.5 (47–201) EDs. FVIII inhibitors were not detected. During XTEND-ed, the mean (standard deviation [SD]) ABRs for Day 1–Month 6 (n=146) was 0.63 (1.6), Months 6–12 (n=144) was 0.77 (1.54), Months 12–18 (n=139) was 0.65 (1.67), and Months 18–24 (n=138) was 0.58 (1.64). The number of participants with zero bleeds for Day 1–Month 6 was 116 of 146 (79.5%), Months 6–12 was 107 of 144 (74.3%), Months 12–18 was 109 of 139 (78.4%), and Months 18–24 was 111 of 138 (80.4%). The mean (95% confidence interval) model-based ABR for the whole efficacy period was 0.64 (0.50; 0.82). Of 205 treated bleeding episodes, 194 (94.6%) resolved with 1 injection of efanesoctocog alfa; participants rated the response as excellent/good for 139/160 (86.9%) bleeds. The median (range) total weekly efanesoctocog alfa consumption was 51.6 (39.4–61.0) IU/kg. The Haem-A-QoL total score and physical health score, analyzed in 102 participants (age: ≥17 years), showed an improvement with mean (SD) change from baseline (XTEND-1) to XTEND-ed Month 24 of -5.8 (13.35) and -7.5 (20.05), respectively. Overall, 117 (80.1%) participants experienced ≥1 treatment-emergent adverse event (TEAE), the most commonly reported being COVID-19 (25.3%), arthralgia (15.1%), and nasopharyngitis (12.3%). Twenty-two participants (15.1%) experienced ≥1 serious TEAE including 2 participants with thromboembolic events: one was a deep vein thrombosis following corrective surgery for a femur fracture (in the setting of treatment with another FVIII product), the other was a cerebral infarction in a participant with pre-existing atrial fibrillation and other risk factors; neither event was related to efanesoctocog alfa treatment.

Conclusion: Long-term results in adults and adolescents in XTEND-ed shows that once-weekly efanesoctocog alfa continues to provide high efficacy and is well tolerated. No inhibitors were detected and ABRs remained low, with continued improvement observed for overall QoL.

Real-World Experience of Switching to Prophylactic Efanesoctocog Alfa in Patients with Moderate and Severe Hemophilia a: An Analysis of the Adelphi Hemophilia Wave III Disease Specific Programme (ASH 2024)

M. Janbain et al

Introduction: Hemophilia A is an inherited condition characterized by a deficiency of clotting factor VIII (FVIII). Efanesoctocog alfa is a first-in-class, once-weekly, high-sustained FVIII replacement therapy. In the XTEND-1 trial, efanesoctocog alfa provided superior bleeding prevention compared with pre-study FVIII prophylaxis treatment, and normal to near-normal FVIII activity for the majority of the week (>40 IU/dL) in patients with severe hemophilia A aged ≥12 years. Treatment outcomes of efanesoctocog alfa in a real-world setting are yet to be reported.

Aim: To use real-world survey data to characterize patients with hemophilia A who switched to prophylactic efanesoctocog alfa and their clinical outcomes.

Methods: This interim analysis of a retrospective, observational study utilized data from the real-world Hemophilia Wave III Disease Specific Programme™, a cross-sectional survey with retrospective data collection capturing linked physician and patient data. A physician-completed patient record form captured clinical and treatment data. Patients in the United States with moderate or severe hemophilia A who had switched from prophylaxis with FVIII replacement therapy or non-factor therapy (emicizumab) to receiving efanesoctocog alfa prophylactically for ≥170 days were included in this analysis. Study objectives were to characterize included patients and to describe their clinical outcomes. Since patients were treated with efanesoctocog alfa for less than 12 months, ABR was estimated using the formula (number of bleeds/days on treatment) x 365 days. Data were collected for this interim analysis from July 2023–June 2024. Descriptive data are reported.

Results: In this interim analysis, 10 physicians provided data for 29 patients receiving efanesoctocog alfa. The mean (standard deviation (SD)) age was 26.4 (8.3; range of 4–49) years, 55% (n=16) of the patients were of white ethnicity; all patients were without inhibitors at the time of survey, with 7% (n=2) previously having had inhibitors; the mean (SD) time since initiating efanesoctocog alfa was 8.8 (2.3) months. Prior to switching to efanesoctocog alfa, most patients (75% (n=21)) were previously treated prophylactically with standard half-life (SHL) FVIII replacement therapy; 18% (n=5) with extended half-life (EHL) FVIII replacement therapy; 4% (n=1) with non-factor therapy (emicizumab); 4% (n=1) with 'other' and 4% (n=1) were not recorded. Physicians reported that the most common reasons for their patients to change from their previous treatment were 'too many infusions/injections' (57% (n=16)), 'more efficacious products available' (43% (n=12)), 'not being effective in preventing ABR' (11% (n=3)) and 'patient felt uncomfortable with the dosing schedule' (11% (n=3)). The most frequently reported reason for prescribing efanesoctocog alfa prophylactically was 'effectiveness in preventing ABR' (76% (n=22)). In the 12 months prior to switching to efanesoctocog alfa treatment, the mean ABR was 1.07 (SD: 2.67; 95% confidence interval (CI) 0.04; 2.16), with 70% (n=19) of patients experiencing no bleeds, 15% (n=4) one bleed, 4% (n=1) 2 bleeds, 4% (n=1) 3 bleeds, 0% (n=0) 4 bleeds and 7% (n=2) five or more bleeds. Ninety-six percent of physicians reported that they were 'completely satisfied' with efanesoctocog alfa for their patients. On efanesoctocog alfa, patients had a mean (SD) dosing interval of 6.9 (0.4) days. The mean (SD) dose of efanesoctocog alfa was 49.3 (3.8) IU/kg. The estimated mean ABR was 0.21 (SD: 0.66; 95% CI -0.04; 0.46). Since the initiation of efanesoctocog alfa treatment 89% (n=25) of patients experienced no bleeds, 4% (n=1) one bleed and 7% (n=2) two bleeds.

Conclusion: Consistent with clinical trial data, this real-world survey supports the effectiveness of switching from factor (SHL or EHL) replacement therapy or emicizumab to efanesoctocog alfa resulting in low bleeding rates. Additionally, most patients do not experience a bleed in the time after switching to efanesoctocog alfa. The frequency and dose of efanesoctocog alfa in a real-world setting is aligned with the United States prescribing information. The limitations of this study were the small sample size and the limited duration of efanesoctocog alfa treatment.These data indicate that in a real-world setting, efanesoctocog alfa provides an effective alternative to existing treatments for hemophilia A, with a once-weekly dosing schedule.

Cost Comparison of Efanesoctocog Alfa with Existing Factor VIII Replacement Therapies for Major Surgeries in People with Severe Hemophilia A (ASH 2024)

J. Staber et al

Introduction: People with severe hemophilia A (HA) are susceptible to excessive bleeds during surgery and insufficient hemostatic control can lead to increased morbidity and mortality. Adequate factor VIII (FVIII) replacement therapy is required pre- and post-operatively to maintain hemostasis, prevent bleeds and facilitate healing. The World Federation of Hemophilia guidelines recommend a pre-operative FVIII level of 80%–100%, and a post-operative FVIII level of 60%–80% on days 1–3, 40%–60% on days 4–6, 30%–50% on days 7–14 for major surgeries in patients with severe HA. Perioperative care with standard half-life (SHL) and extended half-life (EHL) therapies usually require frequent injections to achieve the target FVIII levels, leading to high costs of surgery in patients with severe HA. Efanesoctocog alfa is a first-in-class high-sustained FVIII replacement therapy, designed to prolong half-life by decoupling FVIII from endogenous von Willebrand factor.

Objective: To estimate total costs associated with perioperative hemostatic management in patients with severe HA treated with SHL (octocog alfa), EHL (rurioctocog alfa pegol and efmoroctocog alfa), and high-sustained (efanesoctocog alfa) FVIII replacement therapies.

Methods: Data on dose, total factor consumption, frequency of administration, pre- and post-operative target FVIII level (IU/dL) associated with major surgeries for octocog alfa, rurioctocog alfa pegol, efmoroctocog alfa, and efanesoctocog alfa were collected from United States (US) prescribing information (PI) and phase 3 clinical trials included in PI. The 2024 wholesale acquisition costs (WAC) were used for calculating factor costs. Typically, to achieve the pre-operative target FVIII activity, octocog alfa, rurioctocog alfa pegol, and efmoroctocog alfa are administered every 8–24 hours to prevent bleeding and intermittently for at least another 7 days or until the wound has healed sufficiently. For major surgeries with efanesoctocog alfa, a pre-operative loading dose of 50 IU/kg was administered, followed by 30 or 50 IU/kg every 2 to 3 days, as needed. The total cost was estimated by multiplying the total factor consumed (IU/kg) during the reported perioperative period (7 days for rurioctocog alfa pegol, 14 days for efmoroctocog alfa and efanesoctocog alfa) by the average US adult male weight (assumed as 91 kg) and the cost per IU of SHL, EHL, and high-sustained FVIII replacement therapies used for major surgeries. The difference in total factor consumption and total costs between the therapies were then compared.

Results: Octocog alfa data (NCT00157053) included 58 patients (≥5 years old) with severe HA who underwent 65 surgical procedures (22 major surgeries). Rurioctocog alfa pegol data (NCT01913405) included 21 previously treated male patients (≥12–75 years old) with severe HA who underwent 21 major surgeries. Efmoroctocog alfa data (NCT01454739) included 21 patients (≥12 years old) with severe HA who underwent 23 major surgeries. Efanesoctocog alfa data (NCT04161495) included 12 patients (≥12 years old) with severe HA who underwent 13 major surgeries. The median (interquartile range) total factor consumption (IU/kg) per major surgery during the reported perioperative period for octocog alfa, rurioctocog alfa pegol, efmoroctocog alfa, and efanesoctocog alfa were 910 (228–1825), 629 (464–1457), 493 (121–733), and 163 (45–361), respectively. The total factor cost during the reported perioperative period for major surgery for octocog alfa, rurioctocog alfa pegol, efmoroctocog alfa, and efanesoctocog alfa were $157,339, $142,525, $115,747, and $78,165, respectively. The total factor consumption and cost savings demonstrated by efanesoctocog alfa were compared with SHL and EHL FVIII replacement therapies: 5.5 times fewer IU of factor and $79,174 savings vs octocog alfa, 3.9 times fewer IU of factor and $64,360 savings vs rurioctocog alfa pegol, and 3 times fewer IU of factor and $37,581 savings vs efmoroctocog alfa.

Conclusions: Despite the higher per IU WAC, perioperative management with efanesoctocog alfa was estimated to be less costly than SHL and EHL therapies. This is attributed to its high-sustained factor activity and reduced factor consumption during the reported perioperative period. The major limitations of the study were: the types of major surgeries varied among studies; the perioperative period data of octocog alfa were not found.

Moving towards Normalization of haemostasis and health equity: Evolving treatment goals for haemophilia A (The Official Journal of the World Federation of Haemophilia 2024)

P. André Holme et al

Background: Treatment options for people with haemophilia are evolving at a rapid pace and a range of prophylactic treatment options using various technologies are currently available, each with their own distinct safety and efficacy profile.

Treatment goals: The access to replacement therapy and prophylaxis has driven a dramatic reduction in mortality and resultant increase in life expectancy. Beyond this, the abolition of bleeds and preservation of joint health represent the expected, but rarely attained, goals of haemophilia treatment and care. These outcomes also do not address the complexity of health-related quality of life impacted by haemophilia and its treatment.

Conclusion: Capitalizing on the major potential of therapeutic innovations, 'Normalization' of haemostasis, as a concept, should include the aspiration of enabling individuals to live as normal a life as possible, free from haemophilia-imposed limitations. To achieve this—being supported by the data reviewed in this manuscript—the concept of haemostatic and life Normalization needs to be explored and debated within the wider multidisciplinary teams and haemophilia community.

Efmoroctocog alfa

Long-term efmoroctocog alfa prophylaxis improves perceived pain, mental, and physical health in patients with hemophilia A: *post hoc* analysis of phase III trials using patient-reported outcomes (PubMed 2024)

P. Raheja et al.

Background: Hemophilia-associated bleeding and resultant joint pain and mobility restrictions can predispose patients to poor health-related quality of life (HRQoL). Therefore, efficacy of a treatment needs to address more than just annualized bleed rates.

Methods: Physical health, pain, and HRQoL were assessed by PROs for a cumulative treatment duration of up to ~6 years. The primary endpoint was change from baseline in EuroQoL (EQ)-5D and Haemophilia Quality of Life Questionnaire (Haem-A-QoL).

Results: 118 adult/adolescents and 71 pediatric patients were included. The proportion of adults and adolescents reporting no problem in the EQ-5D analysis of '*pain/discomfort*' significantly increased from A-LONG baseline (35.04%; 41/117) to ASPIRE month 30 (44.68%; 21/47; $p = 0.024$). Mean (standard deviation) Haem-A-QoL subdomain scores for '*feeling*' and '*physical health*' at A-LONG baseline improved by −3.24 (15.13; $p = 0.018$) and −3.85 (23.07; $p = 0.047$), respectively, at study end.

Proportion of pediatric patients reporting no problem on the EQ-5D analysis of '*pain/discomfort*', significantly increased from A-LONG baseline (75.0%; 42/56) to ASPIRE baseline (95.56%; 43/45; p = 0.046). Satisfaction levels for pediatric patients were high at A-LONG baseline and maintained until study end.

Rescue immune tolerance induction with a recombinant factor Fc-fused VIII: prospective RelTIrate study of clinical, humoral and cellular immune responses (PubMed 2024)

C. Königs et al

Background: Immune tolerance induction (ITI) is the gold standard for inhibitor eradication to restore the clinical efficacy of factor replacement therapy in haemophilia. However, as ITI often requires frequent administration over extended periods, it can be considered burdensome for patients and healthcare resources. Therefore, there is a need to optimise ITI treatment, particularly in patients who failed previous ITI attempts.

Objectives: The RelTIrate study aimed to prospectively evaluate rescue ITI with efmoroctocog alfa, an extended half-life recombinant FVIII Fc fusion protein (herein rFVIIIFc), within a limited 60-week timeframe in patients with severe haemophilia A and inhibitors who failed previous ITI attempts.

Design: RelTIrate was a phase IV, open-label, single-arm, interventional, multicentre study.

Results: Nine of 16 enrolled subjects completed the ITI period during RelTIrate, of which one subject attained all 3 ITI success criteria after 46 weeks with no relapse. Two subjects achieved partial success (one subject met 2/3 success criteria; one met all criteria, but not simultaneously, with inhibitor recurrence). One additional subject (ITI failure) achieved negative inhibitor titre. Across these four subjects, median (range) time to negative titre was 19 (11–60) weeks. No new safety concerns were identified. IgG4 was the major contributor to the ADA IgG response. Subjects with partial/complete ITI success had fewer IgG subclasses involved than those who failed/withdrew. Immunophenotyping indicated an increase in regulatory T-cells ($CD4^{+}CD25^{+}CD127^{low}$), supporting the ability to perform sensitive blood sampling to identify immune tolerance markers.

Conclusion: This study demonstrates that ITI with rFVIIIFc given within a limited timeframe has potential benefit in a difficult-to-treat inhibitor haemophilia population who failed previous ITI attempts.

Superior Prophylactic Effectiveness of a Recombinant FVIIIFc Over Standard Half-Life FVIII in Hemophilia A: A-SURE Study (European Journal of Haemophilia 2024)

J. Oldenburg et al

Objectives: The 24-month, prospective, non-interventional, European multicenter A-SURE study evaluated the real-world effectiveness of prophylaxis using an extended half-life recombinant factor VIII (FVIII) Fc fusion protein, efmoroctocog alfa (hereinafter rFVIIIFc), compared with prophylaxis using standard half-life (SHL) FVIII products in patients with haemophilia A.

Methods: Primary endpoints were annualized bleeding rate (ABR), annualized injection frequency, and annualized factor consumption. A comparative study design unique for an observational

hemophilia study was implemented to reduce potential confounding in effectiveness estimates, wherein each patient prescribed rFVIIIFc was matched with one receiving SHL FVIII. Propensity scores were used for adjustment in statistical analyses.

Results: Outcomes for all primary endpoints were significantly better in the rFVIIIFc group (n = 184) compared with the SHL FVIII group (n = 170): mean ABR 1.5 versus 2.3 (difference of −0.8; p = 0.0147); mean annualized injection frequency 114.4 versus 169.2 (difference of −54.8; p < 0.0001); and mean annualized factor consumption 243 024.2 versus 288 718.6 International Units (difference of 45 694.5; p = 0.0003). rFVIIIFc was well tolerated, with no inhibitor development.

Conclusions: rFVIIIFc has superior prophylactic effectiveness versus SHL FVIII, providing higher bleed protection with fewer injections and lower factor consumption.

Gene Therapy

Valoctocogene roxaparvovec (Roctavian)

Efficacy, safety, and quality of life 4 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A in the phase 3 GENEr8-1 trial (PubMed 2024)

A. D. Lewitt et al

Background: Valoctocogene roxaparvovec, an adeno-associated virus-mediated gene therapy for severe hemophilia A, enables endogenous factor (F)VIII expression and provides bleed protection.

Objectives: Determine valoctocogene roxaparvovec durability, efficacy, and safety 4 years after treatment.

Methods: In the phase 3 GENEr8-1 trial, 134 adult male persons with severe hemophilia A without inhibitors and previously using FVIII prophylaxis received a 6×10^{13} vg/kg infusion of valoctocogene roxaparvovec. Efficacy endpoints included annualized bleed rate, annualized FVIII infusion rate, FVIII activity, and the Haemophilia-Specific Quality of Life Questionnaire for Adults. Adverse events and immunosuppressant use were assessed. Change from baseline was assessed after participants discontinued prophylaxis (scheduled for week 4).

Results: Median follow-up was 214.3 weeks; 2 participants discontinued since the previous data cutoff. Declines from baseline in mean treated annualized bleed rate (−82.6%; P < .0001) and annualized FVIII infusion rate (−95.5%; P < .0001) were maintained from previous years in the primary analysis population of 112 participants who enrolled from a noninterventional study. During year 4, 81 of 110 rollover participants experienced 0 treated bleeds. Week 208 mean and median chromogenic FVIII activity were 16.1 IU/dL and 6.7 IU/dL, respectively, in 130 modified intention-to-treat participants. Seven participants resumed prophylaxis since the previous data cutoff. Mean change from baseline to week 208 in Haemophilia-Specific Quality of Life Questionnaire for Adults Total Score (P < .0001) remained clinically meaningful for modified intention-to-treat participants. Alanine aminotransferase elevation was the most common adverse event during year 4 (56/131 participants); none required immunosuppressants.

Conclusions: Valoctocogene roxaparvovec provides persistent FVIII expression, hemostatic control, and health-related quality of life improvements with no new safety signals.

Valoctocogene Roxaparvovec Estimated Long-Term Durability of Treatment Effect: An Extrapolation of the Most Recent Clinical Data (ASH 2024)

S. Santos et al

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

Aims: 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 analyzed 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, median estimated durability is estimated to range from 13.2–20.4 years.

Conclusions: 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.

Giroctocogene Fitelparvovec

Results from the Hemophilia A Cohort of the Non-Investigational Lead-in Study: Prospective Collection of Bleeding Rate in Participants with Hemophilia A Prior to Phase 3 Study (AFFINE) of Giroctocogene Fitelparvovec (ASH 2024)

L. Frenzel et al.

Introduction: Giroctocogene fitelparvovec (PF-07055480) is a liver-directed recombinant adeno-associated virus serotype 6 (AAV6) gene therapy vector encoding a B-domain deleted variant of human factor VIII (FVIII) that enables sustained endogenous FVIII expression. AFFINE (NCT04370054) is an ongoing, pivotal phase 3 trial to evaluate the efficacy and safety of giroctocogene fitelparvovec in individuals with haemophilia A. The primary endpoint of the AFFINE

trial is to demonstrate non-inferiority in total (treated and untreated) annualized bleeding rate (ABR) compared with routine prophylactic FVIII replacement therapy collected prospectively in a separate lead-in trial. We present the results of the lead-in trial initiated to establish prospective bleeding and infusion rates while on FVIII prophylaxis replacement therapy in the usual care setting of participants with hemophilia A. The baseline data obtained in this trial will be used for comparison with data collected post gene therapy for those participants who subsequently enrolled in the giroctocogene fitelparvovec phase 3 AFFINE trial.

Methods: This study (NCT03587116) is a prospective, noninterventional, phase 3 lead-in trial that enrolled adult men 18 to <65 years old with moderately severe to severe hemophilia A (FVIII) on stable prophylaxis FVIII replacement therapy who tested negative for neutralizing antibodies (nAb) to AAV6. The trial is multi-regional in 18 countries in North America, South America, Asia Paci bleeding events in an electronic diary, with most participants providing â‰¥6 months of data prior to entry in the phase 3 AFFINE trial. Selected safety data (serious adverse events [SAEs] and medically important events of FVIII inhibitor, thrombotic events, and factor hypersensitivity reactions) of FVIII replacement therapy were also collected.

Results: In all, 241 patients with hemophilia A were screened and 101 were enrolled in the hemophilia A cohort of this lead-in trial (data for the hemophilia B cohort have been presented previously). The most common reason for screen failure was nAb positivity at screening in 115 (82.1%) of the 140 screen failures. The mean (range) age of those enrolled was 31.8 (18 to 64) years. Most participants were 18-44 years of age (84 [83.2%]), White (78 [77.2%]), and not Hispanic or Latino (76 [75.2%]). Target joints were identi‰¥180 days of follow-up; the mean (SD) follow-up duration of these participants was 351.3 (197.32) days and 23 (22.8%) had â‰¥1 year of follow-up. Overall, 17 (16.8%) participants had <180 days of follow-up; the mean (SD) follow-up duration of these participants was 84.8 (43.64) days. The overall mean (SD) follow-up duration was 306.5 (206.55) days. The mean (SD) total ABR was 6.1 (10.6), mean (SD) treated ABR was 4.87 (7.2), and mean (SD) annualized infusion rate (AIR) was 127.1 (51.8). The mean (SD) annualized total FVIII replacement therapy consumption was 304,998 (153,932) IU. Of the 101 participants, 4 (4.0%) experienced 4 SAEs (hemorrhoidal hemorrhage, upper gastrointestinal hemorrhage, wound infection, and B-cell lymphoma; n=1 [1.0%] each); all SAEs were severe except upper gastrointestinal hemorrhage, which was moderate in severity. No adverse events of special interest were reported, and no safety signals were identified for FVIII replacement therapy.

Conclusions: The ABR and AIR collected in this lead-in trial are representative of FVIII prophylaxis in hemophilia A populations. Although FVIII prophylaxis was well tolerated, with no emerging safety signals, a total ABR of 6.1 illustrates the limitations of current standard of care prophylaxis. The total ABR reported in a subset of participants who went on to enroll in the phase 3 AFFINE trial of giroctocogene noninferiority post gene therapy, in accordance with the AFFINE trial protocol.

Efficacy and Safety of Giroctocogene Fitelparvovec in Adults with Moderately Severe to Severe Hemophilia A: Primary Analysis Results from the Phase 3 AFFINE Gene Therapy Trial (ASH 2024)

A. D. Leavitt et al

Background: Giroctocogene telparvovec (PF-07055480), a hepatocyte-directed recombinant AAV serotype 6 vector encoding a B domain deleted variant of human factor VIII (FVIII), is a single-dose gene therapy aimed at enabling sustained endogenous FVIII expression in individuals with hemophilia

A (HA). We present results from the primary analysis of an ongoing pivotal phase 3 study to evaluate the ecacy and safety of giroctocogene telparvovec in participants with moderately severe to severe HA.

Methods: AFFINE (NCT04370054) is a phase 3, open-label, single-arm trial that enrolled adult men with HA (FVIII:C â‰¤1%) who completed a lead-in study while on exogenous FVIII prophylaxis therapy prior to administration of a single infusion of 3e13 vg/kg giroctocogene telparvovec. Primary and secondary endpoints were assessed in the efficacy population corresponding to participants with 15 months follow-up post infusion and 6 months follow-up in the lead-in study (n=50). The primary endpoint was annualized bleeding rate (ABR) for total (treated and untreated) bleeds from Week 12 (estimated onset of clinically meaningful transgene-derived FVIII levels) through â‰¥15 months (up to data cutoff) post infusion compared with the pre-infusion prophylaxis period. Key secondary endpoints were the percentage of participants with FVIII activity >5% (chromogenic assay) at 15 months and ABR for treated bleeds. Annualized infusion rate (AIR) of exogenous FVIII replacement from Week 12 to 15 months post infusion was a secondary endpoint. Additional secondary endpoints, including the incidence and severity of adverse events (AEs), were assessed for all dosed participants (n=75).

Results: As of June 2024, 75 participants (median age, 30 years [range 19–59]) were dosed with giroctocogene fitelparvovec (median duration of follow-up, 16.8 months [range 7.8–44.4]). Of those, 50 were included in the efficacy population (median duration of follow-up, 33.6 months [range 14.5–44.4]). Within this population, the study met its primary endpoint with a statistically significant decrease (non-inferiority and superiority; 1-sided P=0.004) in total ABR from Week 12 through ≥15 months post infusion vs pre-infusion prophylaxis (mean total ABR, 1.24 vs 4.73; treatment difference, −3.49 [95% CI: −6.06, −0.91]). At Month 15, 84% of participants had FVIII activity >5% (95% CI: 70.9, 92.8; 1-sided P=0.0086 vs null hypothesis of ≤68%). Most participants continued to maintain FVIII activity >5% at later timepoints (82.8% at Year 2 [n=29]). Treated ABR during Week 12 through ≥15 months post infusion was significantly reduced vs prophylaxis (mean treated ABR, 0.07 vs 4.08; treatment difference, −4.01 [95% CI: −5.57, −2.45]; 1-sided P<0.0001), also demonstrating superiority. During the same period, 64% of participants had no bleeds and 88% of participants had no treated bleeds. AIR post infusion was reduced by 99.8% vs the pre-infusion period (mean AIR, 0.2 vs 124.4). At data cutoff, 1 (1.3%) dosed participant had resumed prophylaxis (at 16.1 months post infusion). A total of 624 AEs, mostly mild or moderate, were reported in 74 (98.7%) participants. There were 26 serious AEs (SAEs) in 15 (20%) participants, with pyrexia the most common (n=5 [6.7%]). The most common treatment-related AEs were pyrexia (in 54.7%), alanine aminotransferase (ALT) increased (in 46.7%), and headache (in 38.7%). There have been no study discontinuations. Post infusion, 62.7% of participants received ≥1 dose of corticosteroids due to ALT elevations or decreases in FVIII activity (median time to initiation, 84 days [range 7–193] and mean total time on corticosteroids, 114.6 days [range 11–296]). AEs related to corticosteroids were reported in 19 (25.3%) participants. Transient FVIII activity >150% (defined as ≥1 central chromogenic assay measurement >150%) was reached in 37 (49.3%) participants; based on protocol recommendations and upon investigator's decision, 23 (30.7%) were treated with prophylactic direct oral anticoagulants, which was well tolerated.

Conclusions: Giroctocogene fitelparvovec yielded endogenous FVIII expression in the mild to normal range in most participants, and resulted in superior bleed protection vs routine FVIII prophylaxis and

significant reductions in bleeding. A single infusion was well tolerated and demonstrated durable efficacy on all primary and key secondary endpoints.

Haemophilia B

Replacement therapies

Eftrenonacog alfa (Alprolix)

Real-world usage and effectiveness of recombinant factor VIII/factor IX Fc in hemophilia A/B: final data from the 24-month, prospective, noninterventional PREVENT study in Germany (PubMed 2024)

C. Bidlingmaier et al

Background: Real-world experience with efmoroctocog alfa (a recombinant factor [F]VIII Fc fusion protein [rFVIIIFc]) and eftrenonacog alfa (a recombinant factor IX Fc fusion protein [rFIXFc]) is needed to bridge evidence gaps.

Objectives: To describe rFVIIIFc/rFIXFc usage and effectiveness over a 24-month prospective period.

Methods: PREVENT (NCT03055611), a noninterventional study across 25 German hemophilia treatment centers, enrolled previously treated persons with hemophilia A and B (all ages/severities) on individualized rFVIIIFc/rFIXFc prophylaxis before/at enrollment. Primary endpoints included annualized bleeding rate (ABR), injection frequency (IF), and factor consumption (FC). Additionally, up to 12 months of retrospective FVIII/FIX data were collected. Physician and patient satisfaction, and safety outcomes were also assessed.

Results: Overall, 150 patients received ≥1 rFVIIIFc dose and 47 patients received ≥1 rFIXFc dose, with median prospective follow-up of 20.6 and 21.0 months, respectively. rFVIIIFc/rFIXFc demonstrated low median ABR (0.5/1.7), annualized IF (121.8/52.2 injections/y), and FC (4611.7/2423.9 IU/kg) in line with product labels. Compared with previous FVIII/FIX, there was a 56.0% reduction in ABR for rFVIIIFc (rate ratio, 0.44; 95% CI, 0.31-0.64), with no change for rFIXFc (rate ratio, 0.93; 95% CI, 0.66-1.31); rFVIIIFc/rFIXFc reduced annualized IF (rFVIIIFc, mean difference, −31.7; 95% CI, −40.3 to −23.1; rFIXFc, mean difference, −37.3; 95% CI, −46.9 to −27.8), while FC remained stable (rFVIIIFc, +374.1; 95% CI, +46.8 to +701.3; rFIXFc, +503.9; 95% CI, +95.4 to +912.4). Most physicians and patients were satisfied or highly satisfied with rFVIIIFc/rFIXFc. rFVIIIFc/rFIXFc were well tolerated, with no inhibitor development or treatment-related serious adverse events.

Conclusion: Real-world PREVENT data complement phase 3 trials and show that individualized rFVIIIFc/rFIXFc prophylaxis provided stable bleed protection with low IF and maintained FC. Compared with previous FVIII, ABR was considerably reduced with rFVIIIFc, with stable annualized FC. For rFIXFc, bleed protection was maintained vs previous FIX while reducing annualized IF.

Long-term clinical outcomes of prophylaxis with an rFVIIIFc or rFIXFc in adults aged ≥50 years with hemophilia A or B (ASH 2024)

D. Quon et al

Older people with hemophilia (PwH) who did not receive prophylaxis from a young age are at an increased risk of developing hemophilic arthropathy. Advances in hemophilia care have led to increased life expectancy and resultant challenges in the management of older PwH.2,6-9 Limited guidance exists for managing this population.

Efmoroctocog alfa, a recombinant factor VIII (FVIII) Fc fusion protein (referred to herein as rFVIIIFc), and eftrenonacog alfa, a recombinant FIX Fc fusion protein (rFIXFc), are extended half-life factor replacements for hemophilia A or B, respectively, with demonstrated long-term safety and efficacy among individuals of all ages; however, there are limited data in older PwH.

This post hoc analysis of A-LONG/ASPIRE and B-LONG/B-YOND studies assessed comorbidities and long-term efficacy and safety in those with severe hemophilia aged ≥50 years. Protocols had local ethics board approvals and were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki; participants provided informed consent. A-LONG enrolled previously treated males aged ≥12 years with severe hemophilia A receiving prophylaxis or on on-demand (OD) therapy with ≥12 bleeding events in the 12 months before the study and no history of inhibitors. B-LONG enrolled previously treated males aged ≥12 years with severe hemophilia B on a prior prophylaxis regimen or with ≥8 bleeding events in the 12 months before the study and no history of inhibitors. Eligible participants enrolled in respective extension studies (ASPIRE or B-YOND). Outcomes included annualized bleed rates (ABRs), target joint resolution, modified Hemophilia Joint Health score (mHJHS; A-LONG/ASPIRE), Haemophilia Quality of Life (QoL) Questionnaire for Adults (Haem-A-QoL), factor consumption, cumulative exposure, and safety. Descriptive statistics are presented for participants with an efficacy period. Detailed methods are in supplemental Material. These trials were registered at www.ClinicalTrials.gov (identifiers: NCT01181128, NCT01027364, NCT01454739, and NCT01425723).

There were 21 participants aged ≥50 years in A-LONG, with 20 participating in ASPIRE. At baseline, median age was 57 years, and 81% had target joints (supplemental Table 1). The FVIII regimen before A-LONG was prophylaxis for 29% (6/21) and OD treatment for 71% (15/21). Participants had a median duration of rFVIIIFc treatment of 4.3 years (interquartile range [IQR], 3.1-5.4) and 318 exposure days (IQR, 257-425). In B-LONG, there were 26 participants aged ≥50 years, with 16 participating in B-YOND. The median age at baseline was 56 years, and 62% had target joints (supplemental Table 2). Before B-LONG enrollment, 11 of 26 patients (42%) were treated prophylactically, and 15 of 26 (58%) were treated OD. The median (IQR) duration of rFIXFc treatment was 3.4 years (IQR, 1.0-5.4); 54% had ≥3 years of treatment. The median number of rFIXFc exposure days was 101 (IQR, 44-220).

Prophylaxis with recombinant factor IX Fc fusion protein reduces the risk of bleeding and delays time to first spontaneous bleed event in previously untreated patients with haemophilia B: A post hoc analysis of the PUPs B-LONG study (PubMed 2024)

B. Nolan et al

Objectives: Haemophilia B (HB), characterised by deficient factor IX (FIX), leads to spontaneous bleeds. Severe cases require prophylactic FIX replacement. This post hoc analysis assessed the first spontaneous bleeds among previously untreated patients (PUPs) with HB treated with recombinant FIX Fc fusion protein (rFIXFc) (NCT02234310) to identify factors influencing bleeds.

Methods: Subjects included paediatric PUPs with HB (≤2 IU/dL endogenous FIX). Analyses described treatment patterns (on demand [OD] vs. prophylaxis) and prophylaxis type (started on vs. switched to prophylaxis). Kaplan–Meier analyses assessed the time to first spontaneous bleed, including median time to event and fitting models with predictors for treatment regimen and/or baseline age.

Results: PUPs B-LONG enrolled 33 subjects. Baseline age did not influence the time to first spontaneous bleed for any rFIXFc regimen. Those who started on prophylaxis with rFIXFc (*n* = 11), compared with those treated OD (*n* = 22), had an extended time to first spontaneous bleed. Starting prophylaxis afforded a 93% reduced risk of first spontaneous bleed versus starting OD (hazard ratio [95% confidence interval]: 0.071 [0.009–0.592]) (*p* = .015).

Conclusions: rFIXFc prophylaxis, particularly starting early, reduced the risk of bleeding and delayed time to first spontaneous bleed compared with rFIXFc OD. Hence, initial treatment regimens impact bleed patterns in paediatric PUPs.

Gene Therapy

CSL220 (formely AMT-060)

Stable Factor IX Expression and Sustained Reductions in Factor IX Use 8 Years after Gene Therapy with CSL220 (Formerly AMT-060) in Adults with Hemophilia B (ASH 2024)

F. W. G. Leebeek et al

Introduction: CSL220 (formerly AMT-060) is an adeno-associated virus serotype 5 (AAV5) vector encoding a codon-optimized wild-type human factor IX (FIX) gene, driven by a liver-specific promoter. CSL220 has an identical vector sequence to etranacogene dezaparvovec (CSL222), without the activity-enhancing two nucleotide change in the human FIX coding sequence of the Padua FIX variant. The Phase I/II study included 10 patients with severe or moderately severe hemophilia B (FIX activity ≤2 IU/dL) who received a single intravenous infusion of CSL220 (5×10^{12} gc/kg [Cohort 1; n=5] or 2×10^{13} gc/kg [Cohort 2; n=5]). Nine out of ten patients were FIX concentrate prophylaxis-free after CSL220 administration. Using the one-stage activated partial thromboplastin time (aPTT) assay (HemosIL® SynthASil reagent), mean (standard deviation, SD) and median (range) FIX activities were 6.5 (0.3) IU/dL and 6.5 (6.3–6.7) IU/dL, respectively, in Cohort 1 (n=2) and 6.6 (2.0) IU/dL and 7.2 (3.8–8.3) IU/dL in Cohort 2 (n=4) at completion of the phase I/II trial (NCT02396342), 5 years post-treatment with CSL220. Continued assessment of the efficacy and safety of CSL220 is on-going in an extension study up to 10 years post-administration (NCT05360706).

Methods: Patients who successfully completed all assessments during 5 years of follow-up were enrolled in the open-label, Phase I/IIb extension study. Here, we report the third year of follow-up in the extension study; representing 8 years after CSL220 administration. Four of five patients from Cohort 1 (including one patient who remained on FIX prophylaxis) and all five patients from Cohort 2 enrolled in the extension study.

Results: Endogenous FIX activity (one-stage aPTT assay) remained stable at Year 8; mean (SD) and median (range) FIX activity were 4.9 (1.2) IU/dL and 5.2 (3.6–6.0) IU/dL in Cohort 1 (n=3, excluding

the patient who remained on prophylaxis), and 5.6 (1.2) IU/dL and 5.8 (3.7–7.0) IU/dL in Cohort 2 (n=5), respectively. Mean (SD) annualized bleeding rate (ABR) for individual (excluding the patient who remained on prophylaxis) for Year 8 was 2.2 (2.2, n=3) and 1.0 (1.8, n=5) for Cohort 1 and 2, respectively. In Year 8, one patient in Cohort 1, and three patients in Cohort 2 experienced no bleeds. Mean (SD) annualized spontaneous bleeding rate (AsBR) was 1.5 (1.7, n=3) in Cohort 1 and 0.4 (0.9, n=5) in Cohort 2. Spontaneous bleeds were experienced by two patients in Cohort 1 and one patient in Cohort 2. One patient experienced one traumatic bleed in Cohort 1, and one patient experienced one traumatic bleed in Cohort 2. Mean (SD) annualized FIX consumption during Year 8 (excluding surgeries and the patient who remained on FIX prophylaxis) was 17,817.1 (30,860.1) IU/year (or 189.5 [328.3] IU/kg/year) in Cohort 1 (n=3) and 12,302.4 (24,223.6) IU/year (or 149.3 [300.0] IU/kg/year) in Cohort 2 (n=5). No new safety events were identified during Year 8, and no patient returned to continuous FIX prophylaxis.

Conclusions: Durability of factor expression is a key consideration in the decision-making process about gene therapy for patients and physicians. With just one amino acid difference in the expressed FIX protein, CSL220 is the precursor of etranacogene dezaparvovec (CSL222), which was the first gene therapy approved for the treatment of hemophilia B. This 8-year follow-up after CSL220 administration provides continued evidence for the durability, stability, and safety of FIX expression after AAV5-based gene therapy for the treatment of hemophilia B.

Etranacogene dezaparvovec (Hemgenix)

Invasive procedures and surgery following etranacogene dezaparvovec gene therapy in people with hemophilia B (PubMed 2024)

N. O'Connell et al

Background: Little information regarding the management of invasive procedures in people with hemophilia B (HB) after undergoing gene therapy is available. Here, we report the management of invasive procedures in people with severe or moderately severe HB who had previously been treated with etranacogene dezaparvovec in the phase 2b and phase 3 Health Outcomes with Padua Gene; Evaluation in Hemophilia B clinical trials (NCT03489291 and NCT03569891).

Objectives: The objective of this study was to describe the use of exogenous FIX, endogenous FIX activity prior to invasive procedures, and peri- and postoperative bleeds in participants who underwent invasive procedures after receiving etranacogene dezaparvovec gene therapy.

Methods: This retrospective analysis included invasive procedures performed within 3 and 2 years following a single infusion of 2×10^{13} gc/kg of etranacogene dezaparvovec in participants in the phase 2b and Health Outcomes with Padua Gene; Evaluation in Hemophilia B trials, respectively. Data for factor (F)IX dosing, duration of postoperative FIX use, FIX activity prior to invasive procedures, and postoperative bleeds were collected and analyzed.

Results: The analysis included 64 procedures in 29 participants: 9 major surgeries, 24 minor surgeries, 11 endoscopies, 3 endoscopies with biopsy/polypectomy, and 17 dental procedures. Uncontaminated endogenous FIX activity corresponded to mild hemophilia or normal levels prior to 98% of all procedures, with a median endogenous FIX activity of 43.8 IU/dL (range, 3.1-113 IU/dL). All major surgeries were managed with exogenous FIX, 67% with ≤4 days of FIX infusion. Most minor

surgeries (88%), endoscopies (82%), and dental procedures (94%) were managed with no or a single FIX infusion. Postoperative bleeds occurred after 1 minor surgery and 4 dental procedures. There were no symptomatic thrombotic events or FIX inhibitor developments.

Conclusion: Etranacogene dezaparvovec has the potential to facilitate perioperative management in people with HB by reducing the need for perioperative exogenous FIX and its associated risks.

Analysis of long-term clinical and cost impact of etranacogene dezaparvovec for the treatment of hemophilia B population in the United States (PubMed 2024)

S; Yan et al

Introduction: Etranacogene dezaparvovec (EDZ), Hemgenix, is a gene therapy recently approved for people with hemophilia B (PwHB).

Objective: To estimate long-term clinical impact and cost of EDZ in the United States (US).

Methods: A decision-analytic model was developed to evaluate the long-term impact of introducing EDZ for PwHB over a 20-year time horizon. Factor IX (FIX) prophylaxis comparator was a weighted average of different FIX prophylaxis regimens based on US market share data. We compared a scenario in which EDZ is introduced in the US versus a scenario without EDZ. Clinical inputs (annualized FIX-treated bleed rate; adverse event rates) were obtained from HOPE-B phase 3 trial. EDZ durability input was sourced from an analysis predicting long-term FIX activity with EDZ. EDZ one-time price was assumed at $3.5 million. Other medical costs, including FIX prophylaxis, disease monitoring, bleed management, and adverse events were from literature. The model estimated annual and cumulative costs, treated bleeds, and joint procedures over 20 years from EDZ introduction.

Results: Approximately 596 PwHB were eligible for EDZ. EDZ uptake was estimated to avert 11,282 bleeds and 64 joint procedures over 20 years. Although adopting EDZ resulted in an annual excess cost over years 1-5 (mean: $53 million annually, total $265 million), annual cost savings were achieved beginning in year 6 (mean: $172 million annually; total $2.58 billion in years 6-20). The total cumulative 20-year cost savings was $2.32 billion, with cumulative cost savings beginning in year 8.

Conclusion: Introducing EDZ to treat PwHB is expected to result in cost savings and patient benefit over 20 years. Initiating PwHB on EDZ sooner can produce greater and earlier savings and additional bleeds avoided. These results may be a conservative estimate of the full value of EDZ, as PwHB would continue to accrue savings beyond 20 years.

Fidanacogene elaparvovec (brand names Durveqtix, Beqvez)

In Vitro and In Vivo Potency Differences between AAVRh74var and AAV5 Vectors Encoding the Same High-Activity Human Factor IX Variant, FIX-R338L, Expression Cassette: Implications for Hemophilia B Gene Therapy (ASH 2024)

D. D. Pittman et al

Background: Fidanacogene elaparvovec is a non-replicating, recombinant adeno-associated virus (AAV)-based gene therapy vector that utilizes AAVRh74var (derived from a naturally occurring AAVRh74), to transfer a high-activity variant of human factor IX (FIX) FIX-R338L for the treatment of hemophilia B (HB). Data from the ongoing phase 3 BENEGENE-2 study demonstrated FIX activity levels in the mild hemophilia to normal range and a 71% reduction in annualized bleeding rate in participants with HB treated with danacogene elaparvovec. Fidanacogene elaparvovec 5×10 vg/kg was recently approved for use in Canada, the United States and Europe. The only other approved HB gene therapy (etranacogene dezaparvovec) utilizes the AAV5 capsid and is administered at a 40-fold higher dose (2×10 gc/kg). In vitro and in vivo studies evaluated whether the AAVRh74var capsid confers a higher transduction eciency, relative to AAV5, thus potentially allowing for lower overall AAV capsid dosing to achieve comparable FIX activity levels in patients with HB.

Methods: The vector genome of danacogene elaparvovec (including the FIX-R338L transgene, AAV2 inverted terminal repeats [ITRs], genetic control elements, intron and polyA signal) was packaged into either the AAVRh74var or AAV5 capsid using an HEK293 cellular production system. A molecular assessment demonstrated AAVRh74var FIX-R338L and AAV5 FIX-R338L preparations were similar in empty/full capsid ratio, viral protein (VP)1/2/3 ratio, and purity. In an in vitro study, the Huh7 human-derived hepatocellular carcinoma cell line was transduced with increasing concentrations of AAVRh74var FIX-R338L or AAV5 FIX-R338L ranging from 1.6×10 to 1.0×10 vg/cell. FIX activity in conditioned cell growth medium was assessed 96 and 120 hours post transduction. Each concentration was tested in duplicate in 2 independent experiments. After removal of the conditioned medium for FIX activity determination at 120 hours post transduction, cells from a single transduction were lysed and RNA was extracted. In an in vivo mouse model of HB, male mice (10 mice/group) received a single intravenous injection of AAV5 FIX-R388L or AAVRh74var FIX-R388L diluted in PBS to achieve 4×10 or 1×10 vg/kg or PBS alone (control). Blood and tissues were harvested at Weeks 1 and 4 post treatment. In the in vitro and in vivo studies, FIX activity was determined using the one-stage activated partial thromboplastin time (aPTT) clotting assay. FIX mRNA expression and vector genomes were determined by digital droplet PCR. All procedures performed in animals were reviewed and approved by an Institutional Animal Care and Use Committee.

Results: In Huh7 cells, a dose-dependent increase in FIX activity was observed with both AAV vectors, with similar trends in FIX activity observed at 96 and 120 hours post transduction. AAVRh74var FIX-R338L exhibited an increase in potency at all concentrations tested (potency difference of AAVRh74var FIX-R338L vs AAV5 FIX-R338L at 1.0×10 vg/cell: 6.66- to 10.57- fold). FIX mRNA expression levels were greater with AAVRh74var FIX-R338L vs AAV5 FIX-R338L. HB mice dosed with 4×10 vg/kg had a mean FIX activity of 0.119 IU/mL vs 0.007 IU/mL with AAVRh74var FIX-R338L vs AAV5 FIX-R338L. Mean FIX activity was >100x higher with AAVRh74var FIX-R338L vs AAV5 FIX-R338L in mice dosed with 1×10 vg/kg when assessed at both timepoints (Weeks 1 and 4). Liver mRNA levels were consistent with FIX activity. FIX expression was consistently higher in mice that received AAVRh74var FIX-R338L compared with AAV5 FIX-R338L. FIX expression was very low in the AAV5 FIX-R338L-treated mice. Liver vector genome copies at 4 weeks post treatment were higher in the AAVRh74var FIXR338L compared with AAV5 FIX-R338L treated mice.

Conclusions: In this head-to-head potency comparison in the Huh-7 human liver cell line and male HB mice, AAVRh74var had a higher transduction potency compared with AAV5. FIX-R338L activity and liver mRNA expression levels were higher in mice that received AAVRh74var FIX-R338L vs AAV5

FIX-R338L. These results demonstrate capsid selection can impact intended infectivity and the mechanism of cellular uptake. Overall, the results demonstrate differences between the AAVRh74var and AAV5 capsids. This is consistent with danacogene elaparvovec (AAVRh74var) achieving clinically robust ecacy, despite a several-fold lower dose than AAV5-based gene therapies.

Use of Fidanacogene Elaparvovec, a Gene Therapy Vector, to Deliver a Stable, Fully Functional Human Factor IX Transgene for the Treatment of Hemophilia B: A Combined Analysis of Safety (ASH 2024)

B. Samelson-Jones et. Al

Background: Fidanacogene elaparvovec is a non-replicating, recombinant, liver-tropic, adeno-associated virus-based (rAAV) gene therapy that transfers a high-activity variant of human factor IX (FIX) FIX-R338L for the treatment of hemophilia B (HB). Data from a phase 1/2a danacogene elaparvovec trial and its long-term follow-up (LTFU) demonstrated sustained FIX activity in the mild hemophilia to normal range, with low bleeding rates and a reduction in FIX infusions up to 6 years post dosing. In the ongoing, phase 3 BENEGENE-2 trial, danacogene elaparvovec resulted in FIX activity levels in the mild hemophilia to normal range and a reduction in annualized bleeding rate up to 4 years post dosing. Fidanacogene elaparvovec was recently approved for use in Canada, the United States, and Europe. As a novel therapeutic modality, the long-term safety of rAAV hemophilia gene therapies is unknown. To address this, we report a combined analysis of danacogene elaparvovec safety across its clinical development.

Methods: Data from the phase 1/2a trial (NCT02484092, completed), its LTFU study (NCT03307980, cutoff August 15, 2023), and the BENEGENE-2 trial (NCT03861273, cutoff August 30, 2023) were included. Men â‰¥18 years with HB (FIX â‰¤2%) received a single intravenous infusion of 5Ã—10 vg/kg danacogene elaparvovec. Patients with AAV capsid neutralizing antibodies, baseline alanine transaminase (ALT) or aspartate transaminase (AST) >2Ã— upper limit of normal (ULN) or bilirubin >1.5Ã— ULN were excluded. Safety endpoints included adverse events (AEs) and serious AEs (SAEs) in the rst year post dosing. In the subsequent follow-up after Year 1, non-serious gene therapy-related AEs were reported together with SAEs. AEs of special interest (hypersensitivity reactions, thrombotic events, FIX inhibitors, hepatic malignancies, elevated transaminases), clinical laboratory results, and hepatic evaluations were included. Participants were followed for up to 6 years.

Results: Data from 60 unique participants (phase 1/2a, n=15 dosed; L TFU for those dosed in phase 1/2a, n=14; BENEGENE-2, n=45 dosed) who received for phase 1/2a and its L TFU and 2.8 (range 1.2â€“4.0) years for BENEGENE-2. The total safety experience was based on 204.8 participant-years of follow-up. All participants have >1 year of follow-up, 54 (90%) >2 years, and 29 (48%) >3 years. Most participants had severe HB (80% with FIX activity <1%), 75% were White, with median age of 30.5 (range 18â€“62) years, and median body mass index (BMI) 28 (range 18â€“48) kg/m 2 at baseline. In the increased AL T (n=12 [20%]; mild, n=9; moderate, n=3) and nasopharyngitis (n=11 [18%]; mild, n=8; moderate, n=3). In the total follow-up period, 52/60 (87%) participants had AEs and 11 (18%) had SAEs. The most frequently reported AE was increased AL T (n=12 [20%]) and SAE of anemia (n=2 [3%]). Age, BMI and geographic region had no impact on the incidence of AEs. In the decreased FIX levels (median duration 98 [range, 41â€“276] days). All corticosteroid treatments were completed within 1 year post gene therapy. No participants initiated corticosteroid treatment after 1

year. With up to 6 yearsâ€™ follow-up, there have been no FIX inhibitors or hepatic malignancies, and no gene therapy-related elevated transaminases that failed to improve/resolve with immunosuppressive treatment. Overall, 11 (18%) participants had mild-to-moderate events within the scope of hypersensitivity; no acute hypersensitivity events or infusion-related reactions were assessed as related to fidanacogene elaparvovec. There were no deaths or discontinuations due to an AE. Liver ultrasounds from Year 1 of the LTFU study onwards showed 4 participants had steatosis and 1 had cirrhosis; 1 participant in BENEGENE-2 had hepatic stenosis/polycystic kidney disease and 1 had a polyp in the gall bladder. None of these ndings were considered related to gene therapy.

Conclusion: This combined analysis demonstrates the favorable safety prole of fidanacogene elaparvovec in the largest dataset with the longest follow-up for an HB gene therapy. LTFU will continue for up to 15 years.

Gene Therapy with Fidanacogene Elaparvovec in Adults with Hemophilia B (PubMed 2024)

E. Cuker et al

Background: Fidanacogene elaparvovec, an adeno-associated virus (AAV) gene-therapy vector for hemophilia B containing a high-activity human factor IX variant (FIX-R338L/ FIX-Padua), was associated with sustained factor IX activity in a phase 1–2a study.

Methods: We conducted a phase 3 open-label study of fidanacogene elaparvovec at a dose of 5×1011 vector genome copies per kilogram of body weight. Men 18 to 65 years of age with hemophilia B and a factor IX level of 2% or less were eligible for screening if they had received at least 6 months of therapy with prophylactic factor IX concentrate. The primary end point, tested for noninferiority, was the annualized bleeding rate (treated and untreated bleeding episodes) from week 12 to month 15 after treatment with fidanacogene elaparvovec as compared with the prophylaxis lead-in period. Superiority, additional efficacy end points, and safety were also assessed.

Results: Of 316 men who underwent screening for the lead-in study, 204 (64.6%) were not eligible; 188 (59.5%) of those were ineligible owing to the presence of anti-AAV neutralizing antibodies. Of the 45 participants who received fidanacogene elaparvovec, 44 completed at least 15 months of follow-up. The annualized rate of bleeding for all bleeding episodes decreased by 71%, from 4.42 (95% confidence interval [CI], 1.80 to 7.05) at baseline to 1.28 (95% CI, 0.57 to 1.98) after gene therapy, a treatment difference of −3.15 episodes (95% CI, −5.46 to −0.83; P=0.008). This result shows the noninferiority and superiority of fidanacogene elaparvovec to prophylaxis. At 15 months, the mean factor IX activity was 26.9% (median, 22.9%; range, 1.9 to 119.0) by one-stage SynthASil assay. A total of 28 participants (62%) received glucocorticoids for increased aminotransferase levels or decreased factor IX levels (or both) starting between 11 and 123 days. No infusion-related serious adverse events, thrombotic events, development of factor IX inhibitors, or malignant conditions were observed.

Conclusions: Fidanacogene elaparvovec was superior to prophylaxis for the treatment of participants with hemophilia B, leading to reduced bleeding and stable factor IX expression. (Funded by Pfizer; BENEGENE-2 ClinicalTrials.gov number, NCT03861273.)

Bypassing Agents

Real-world effectiveness of eptacog beta in patients with haemophilia and inhibitors: A multi-institutional case series (PubMed 2024)

K Youkhana et al.

Introduction: The management of bleeding events (BEs) in haemophilia A (HA) and B (HB) patients with inhibitors necessitates the use of bypassing agents. The recombinant factor VIIa bypassing agent eptacog beta has demonstrated efficacy at treating BEs and managing perioperative bleeding in adults in phase three clinical studies.

Aims: To provide real-world descriptions of eptacog beta use for BE treatment in patients on emicizumab or eptacog beta prophylaxis.

Methods: Twenty-four spontaneous and traumatic BEs are described (muscle hematomas, joint hemarthroses, port site, and epistaxis) involving 11 subjects. Eptacog beta was effective for acute bleed treatment as both first-line therapy and for treatment of BEs refractory to eptacog alfa in 23/24 events. When eptacog beta was used for prophylaxis, 2/3 patients reported a decreased frequency of breakthrough BEs compared with prophylactic eptacog alfa and one patient experienced a similar frequency of breakthrough BEs compared with prophylactic activated prothrombin complex concentrate. Eptacog beta provided effective bleed control for three subjects who underwent minor surgical procedures. Treatment with eptacog beta was estimated to be 46%–72% more cost-effective than eptacog alfa. No safety concerns or adverse events were reported.

Conclusions: In this case series, eptacog beta was safe, effective, and economical as first-line therapy, treatment of refractory BEs, management of perioperative bleeding, or prophylaxis in haemophilia patients with inhibitors.

Re-balancing Therapies

Concizumab (brand name Alhemo)

Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial (PubMed 2024)

P. Chowdary

Background: Concizumab is an anti-tissue factor pathway inhibitor monoclonal antibody in development as a once-daily, subcutaneous prophylaxis for patients with haemophilia A or haemophilia B with or without inhibitors. We aimed to assess the efficacy and safety of concizumab in patients with haemophilia A or B without inhibitors. Here we report the results from the confirmatory analysis cutoff.

Methods: This prospective, multicentre, open-label, randomised, phase 3a trial (explorer8) was conducted at 69 investigational sites in 31 countries. Eligible patients were male, aged 12 years or older, and had congenital severe haemophilia A or moderate or severe haemophilia B without inhibitors and with documented treatment with clotting factor concentrate in the 24 weeks before screening. The trial was paused because of non-fatal thromboembolic events in three patients (two from this trial [explorer8] and one from a related trial in haemophilia with inhibitors [explorer7; NCT04083781]) and restarted with mitigation measures, including a revised dosing regimen of subcutaneous concizumab at 1·0 mg/kg loading dose on day 1 and subsequent daily doses of 0·20 mg/kg from day 2, with options to decrease to 0·15 mg/kg, stay on 0·20 mg/kg, or increase to 0·25 mg/kg on the basis of concizumab plasma concentration measured after 4 weeks on concizumab. Patients recruited after treatment restart were randomly assigned 1:2 using an interactive web response system to receive no prophylaxis and continue on-demand clotting factor (group 1) or concizumab prophylaxis (group 2). The primary endpoints were the number of treated spontaneous and traumatic bleeding episodes for patients with haemophilia A and haemophilia B separately, assessed at the confirmatory analysis cutoff in randomly assigned patients. Analyses were by intention-to-treat. There were two additional groups containing non-randomly-assigned patients: group 3 contained patients who entered the trial before the trial pause and were receiving concizumab in the phase 2 trial (explorer5; NCT03196297), and group 4 contained patients who received previous clotting factor concentrate prophylaxis or on-demand treatment in the non-interventional trial (explorer6; NCT03741881), patients randomly assigned to groups 1 or 2 before the treatment pause, and patients from explorer5 enrolled after the treatment pause. The safety analysis set contained all patients who received concizumab. Superiority of concizumab over no prophylaxis was established if the two-sided 95% CI of the treatment ratio was less than 1 for haemophilia A and for haemophilia B. This trial is registered with ClinicalTrials.gov, NCT04082429, and its extension part is ongoing.

Findings: Patients were recruited between Nov 13, 2019 and Nov 30, 2021; the cutoff date for the analyses presented was July 12, 2022. 173 patients were screened, of whom 148 (86%) were randomly assigned or allocated to the four groups in the study after trial restart on Sept 30, 2020 (nine with haemophilia A and 12 with haemophilia B in group 1; 18 with haemophilia A and 24 with haemophilia B in group 2; nine with haemophilia A in group 3; and 46 with haemophilia A and 30 with haemophilia B in group 4). The estimated mean annualised bleeding rate ratio for treated spontaneous and traumatic bleeding episodes during concizumab prophylaxis versus no prophylaxis was 0·14 (95% CI 0·07–0·29; p<0·0001) for patients with haemophilia A and 0·21 (0·10–0·45; p<0·0001) for patients with haemophilia B. The most frequent adverse events in patients who received concizumab were SARS-CoV-2 infection (19 [13%] of 151 patients), an increase in fibrin D-dimers (12 [8%] patients), and upper respiratory tract infection (ten [7%] patients). There was one fatal adverse event possibly related to treatment (intra-abdominal haemorrhage in a patient from group 4 with haemophilia A with a long-standing history of hypertension). No thromboembolic events were reported between the trial restart and confirmatory analysis cutoff.

Interpretation: Concizumab was effective in reducing the bleeding rate compared with no prophylaxis and was considered safe in patients with haemophilia A or B without inhibitors. The results of this trial suggest that concizumab has the potential to be one of the first subcutaneous treatment options for patients with haemophilia B without inhibitors.

Annualized Bleeding Rates in Patients with Hemophilia a or B and Inhibitors with and without Target Joints at Baseline: Results from the Concizumab Phase 3 Explorer7 Study (ASH 2024)

A. D. Shapiro et al

Background: In patients with hemophilia, recurring bleeds into the same joint, known as target joint, cause hemophilic arthropathy and reduce quality of life. Prophylaxis is the current standard of care for severe hemophilia, started early in life to prevent onset and progression of joint damage by reducing recurrent bleeds, allowing patients to participate in physical and social activities, and improve their quality of life. Concizumab is a recombinant anti-tissue factor pathway inhibitor monoclonal antibody under development as a once-daily subcutaneous prophylaxis for hemophilia A/B with and without inhibitors. Here, we present the annualized bleeding rate (ABR) results in patients with hemophilia A/B with inhibitors (HAwI/HBwI), with or without target joints at baseline, from the prospective, multicenter, open-label, phase 3 explorer7 (NCT04083781) study.

Aim: To assess the ABR in patients with HAwI/HBwI, with or without target joints at baseline, during concizumab prophylaxis vs on-demand treatment.

Methods: Target joints were defined as ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period; target joints were deemed resolved when there had been ≤2 bleeds in the joint during the previous 12 months (Blanchette VS et al. J Thromb Haemost. 2014;12(11):1935–39). Treated spontaneous and traumatic bleeding episodes were assessed at the 32- and 56-week cut-offs for patients with and without target joints at baseline. The 32- and 56-week cut-offs were defined as when all patients had completed the visit after 32 or 56 weeks respectively, or permanently discontinued treatment. In the explorer7 study, patients with HAwI/HBwI were randomized 1:2 to on-demand treatment (arm 1; ≥24 weeks) or concizumab prophylaxis (arm 2; ≥32 weeks), or assigned to non-randomized concizumab prophylaxis arms 3 and 4. After ≥24 (arm 1) or ≥32 weeks (arm 2–4), all patients were offered entry into the extension part, and patients in arm 1 switched to concizumab prophylaxis. Patients received a 1.0 mg/kg concizumab loading dose on Day 1, followed by an initial 0.20 mg/kg daily dose starting on Day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 4. Results for estimated mean ABRs are presented for arm 2 vs arm 1; descriptive results are presented for all patients (arms 1–4). Informed consent/ethics committee approval were obtained.

Results: Male patients (≥12 years) with HAwI/HBwI were recruited (2.3% American Indian/Alaska Native, 27.8% Asian, 6.8% Black/African American, 58.6% White, 4.5% not reported). Of the 133 patients enrolled (HAwI: 80; HBwI: 53), 19 were randomized to on-demand treatment (arm 1), 33 randomized to concizumab prophylaxis (arm 2), and 81 allocated to concizumab prophylaxis (arms 3/4). After the 32-week cut-off, 13 patients from arm 1 switched to concizumab prophylaxis. A total of 104 patients in arms 1–4 completed treatment at the 56-week cut-off.

At the 32-week cut-off, for patients with target joints at baseline, estimated mean ABR (95% confidence interval [CI]) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis (arm 2) was 1.7 (0.55–5.51) vs 10.6 (4.18–26.92) on-demand (arm 1); ABR ratio was 0.16 (0.06–0.48; P=0.001), indicating an 84% reduction in bleeding episodes. For patients with no target joints at baseline, estimated mean ABR (95% CI) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis (arm 2) was 0.9 (0.48–1.58) vs 9.0 (5.59–14.53) on-demand (arm 1); ABR ratio was 0.10 (0.05–0.19; P<0.001), indicating a 90% reduction in bleeding episodes.

At the 32-week cut-off, overall median ABR (interquartile range [IQR]) during concizumab prophylaxis (arms 1–4) in patients with and without target joints at baseline, for treated spontaneous and traumatic bleeding episodes was 0.9 (0.0–4.3) and 0.0 (0.0–2.8), for joint bleeding episodes 0.0 (0.0–3.9) and 0.0 (0.0–1.5), and for target joint bleeding episodes 0.0 (0.0–1.1) and 0.0 (0.0–0.0), respectively. By the 56-week cut-off, 92% of target joints had resolved (arms 1–4), and low median ABRs were maintained on concizumab. Overall safety data showed no new findings.

Conclusions: In the explorer7 study, once-daily, subcutaneous concizumab prophylaxis effectively reduced ABR irrespective of the presence of target joints at baseline at the 32-week cut-off, and low ABRs were maintained at the 56-week cut-off.

Marstacimab

Patient and Caregiver Preferences for Hemophilia Prophylactic Treatments: A Discrete Choice Experiment (The Official Journal of World Federation of Haemophilia 2024)

H. Lu et al

Background: The expansion of hemophilia treatment to include non-factor prophylaxis provides new treatment options for people living with hemophilia (PwH). The objective of this study was to measure PwH and caregiver (CG) preferences regarding hemophilia A (HA) and B (HB) prophylaxis, their willingness to trade-off benefits and risks, and their preferences for administration and device types.

Methods: A cross-sectional, web-based survey including a discrete choice experiment (DCE) was administered to adult PwH and CGs of children (aged 8 to 17 years) with hemophilia in the US and UK. The DCE design was informed by an evidence review and consultations with a steering committee of clinical and patient advisors. The survey was pre-tested in cognitive interviews with 10 PwH and 10 CGs prior to launch. In the DCE, each participant completed 10 choice tasks, each presenting two hypothetical prophylaxis profiles described by seven attributes. The attributes included two benefits (change in the number of annual bleeds, requirement for a second treatment for breakthrough bleeds), two risks during the next year of treatment (serious side effects, developing inhibitors), and three additional treatment characteristics (administration and device type, dosing frequency, refrigeration requirement). DCE responses were analyzed using a mixed logit model. Hemophilia types and country of residence were pooled for analysis for both PwH and CGs. Relative attribute importance (RAI) scores were calculated to assess the relative impact of improving each attribute from the worst to the best level on overall treatment preference. In addition, the trade-offs participants were willing to accept to change administration and device type were calculated.

Results: A total of 194 PwH and 169 CGs participated. The mean age of PwH was 38.5 years (range 18-80), the majority (95%) were male, White (78%), and had HA (85%). Over half (59%) were on factor replacement therapy, 43% were on non-factor prophylaxis. The mean age of CGs was 43.3 years (range 22-71), the majority were female (84%). Of the children with hemophilia they cared for, the mean age was 12.6 years (range 8 – 17), the majority were male (97%), White (69%) and had HA (80%). Among the children, 56% were on factor replacement, 47% were on non-factor prophylaxis. The attributes had similar impacts on treatment preferences of both PwH and CGs. Both considered treatment frequency (change from daily to every two to four weeks) to be the most important

attribute (RAI: PwH 31.3%; CG 36.6%), followed by change in the number of annual bleeds (change from 2 more bleeds to 3 fewer bleeds; RAI: PwH 23.6%; CG 21.7%). Risk of serious side effects (change from 5% to 0%; RAI: PwH 13.3%; CG 12%), administration and device type (change from intravenous (IV) infusion to subcutaneous (SC) injection via pre-filled pen (PFP); RAI: PwH 12.1%; CG 10.4%), and risk of developing inhibitors (change from 5% to 0%; RAI: PwH 11.8%; CG 11.2%), had a similar impact on preferences, each being approximately one third as important as treatment frequency and half as important as change in annual bleeds. Refrigeration requirements (change from until use to up to 30 days; RAI: PwH 7.7%; CG 6.9%) were less important, although both PwH and CGs preferred to avoid treatments requiring refrigeration until use. The need for a second treatment for breakthrough bleeds (change from required to not required; RAI: PwH 0.3%; CG 1.1%) was unimportant to both PwH and CGs. With regard to administration and device type, both PwH and CGs preferred SC injections to IV infusions (P<0.001 for both groups). SC injection using a pre-filled pen (PFP) was numerically preferred to SC injection using a vial and syringe; however, this finding was not statistically significant. PwH were willing to accept a 2.9 % increase in risk of serious side effects in the next year, or a 3.1% increase in risk of developing inhibitors in the next year, to have SC injection via PFP rather than IV infusion.

Conclusions: Both PwH and CGs highly valued avoiding daily treatment administration and were willing to accept reduced benefits or increased risks in exchange for SC administration of prophylaxis via a PFP or vial and syringe device instead of IV infusion. Understanding preferences for hemophilia treatments and the trade-offs that PwH and CGs are willing to make between treatment attributes may facilitate shared decision-making when selecting prophylactic options.

Safety Biomarkers in Participants With Severe Hemophilia A or Moderately Severe to Severe Hemophilia B Without Inhibitors Receiving Prophylactic Marstacimab Treatment: Results From the Phase 3 BASIS Trial (ASH 2024)

C. Turich Taylor et al

Background: Marstacimab is a human monoclonal antibody targeted to the K2 domain of tissue factor pathway inhibitor (TFPI) to improve hemostasis through the extrinsic coagulation pathway. BASIS (NCT03938792) is an ongoing one-way, cross-over, open-label, multicenter, pivotal phase 3 study of marstacimab in participants with severe (factor VIII [FVIII] <1%) hemophilia A (HA) or moderately severe to severe (factor IX [FIX] ≤2%) hemophilia B (HB) with or without inhibitors. The efficacy and safety of marstacimab administration up to 450 mg once-weekly (QW) has been previously demonstrated in BASIS and previous phase 1/2 studies. Here, we present safety biomarker data from the BASIS study.

Methods: BASIS enrolled males aged ≥12–<75 years with severe HA or moderately severe to severe HB. Here, we report results for the non-inhibitor cohort (the inhibitor cohort is ongoing). Participants entered a 6-month observational phase (OP) wherein they received their prescribed factor replacement therapy: on-demand (OD) or routine prophylaxis (RP). Participants then crossed over to the 12-month active treatment phase (ATP) and received a single loading dose of 300 mg marstacimab (2×150 mg subcutaneous [SC] injections) followed by 150 mg SC QW. Safety assessments included monitoring changes from baseline (CFB) during the OP (to day 60) and ATP (to day 360) in biomarker profiles for: red blood cell count (hemoglobin and hematocrit), coagulation (activated partial thromboplastin time [aPTT], prothrombin time, fibrinogen, and platelet count),

hepatic function (liver function tests [LFTs]), renal function (serum creatinine), cardiac function (troponin I), and inflammation (leukocyte count). Blood samples were collected at OP baseline (day 1), and day 0 (baseline, pre-dose), 60, 180, 300 and 360 of the ATP to generate data on safety biomarkers and were analyzed descriptively.

Results: A total of 128 participants (median age, 30 [range 13–66] years) entered the OP (n: OD: HA 29, HB 8; RP: HA 72, HB 19) and 116 (n: OD 33, RP 83) were treated with marstacimab in the ATP. The mean (range) treatment duration with marstacimab was 12.1 (11.5–13.1) months for the OD group and 11.6 (0.9–12.8) months for RP group in the ATP. For both groups, mean hemoglobin and hematocrit either remained stable or improved during the ATP compared with the OP. Marstacimab did not result in CFBs in mean (SD; range) prothrombin time for the OD (0.1 seconds [0.6; -1.1–1.6]) and RP groups (0.2 seconds [0.6; -0.9–1.4]). The mean (SD; range) aPTT increased for the OD group from ATP day 0 (56.9 sec [9.5]; 36.0–81.7) to ATP day 360 (62.5 sec [18.19; 39.7–151.0]) with a change of 6.5 sec (14.6; -22.5–69.9), and increased for the RP group from ATP day 0 (50.9 sec [9.35; 33.8–65.3] to ATP day 360 (59.4 sec [13.74; 30.4–116.8]) with a CFB of 7.8 sec (13.3; -17.0–69.9). For most participants, fibrinogen values were normal in the OP and a small mean (SD; range) decrease from baseline was observed in both the OD (-0.2 g/L [0.48; -0.8–0.7]) and RP groups (-0.2g/L [0.64; -1.6–1.0] during the ATP. A decrease in mean (SD; range) platelet count from baseline was observed for the OD group (-15.6 [47.9 -132.0–91.0]) and maintained for the RP group (-0.7 [45.0; -96.0–177.0]) with values remaining within the normal range for most participants throughout the OP and ATP. Most LFT values were similar between the OP and ATP, with minimal CFB in both groups. Hyperbilirubinemia was observed for 2 participants (OD n=1, RP n=1). Troponin I levels were within the normal range during the OP and no participants developed elevated levels above normal with marstacimab. Leukocyte count values were normal in most participants over the OP and ATP. Across all parameters, none of the laboratory test abnormalities were considered clinically significant or reported as adverse events by the investigator.

Conclusions: Overall, evaluation of CFB for safety biomarkers showed no clinically important findings in participants with severe HA or moderately severe to severe HB. Parameters indicative of red blood cell count (hemoglobin and hematocrit) either remained stable or improved with marstacimab, and small decreases in fibrinogen were consistent with the mode of action of marstacimab. There was no clinically meaningful impact on aPTT. There were no reported adverse events related to CFB in safety biomarkers in any participants.

Descriptive Characterization of Bleeding Events in Participants with Severe Hemophilia A or B without Inhibitors, Receiving Prophylactic Marstacimab Treatment (ASH 2024)

D. Matino et al.

Background: Marstacimab is a monoclonal antibody targeted to the K2 domain of tissue factor pathway inhibitor to reduce inhibition of the extrinsic coagulation pathway and rebalance hemostasis independently of factor VIII (FVIII) and factor IX (FIX) activity. Previous phase 1 and 2 studies have demonstrated the efficacy and safety of subcutaneous (SC) marstacimab prophylaxis up to 450 mg once weekly (QW) to reduce bleeding events in adults with hemophilia A (HA) or hemophilia B (HB), with or without inhibitors. The ongoing pivotal phase 3 BASIS study (NCT03938792) demonstrated 150 mg SC QW marstacimab was effective in reducing treated bleeds vs prior on-demand (OD) or routine prophylaxis (RP) therapy in participants (pts) with severe HA (FVIII <1%) or moderately

severe to severe HB (FIX ≤2%) without inhibitors. Contemporary hemophilia trials typically report treated bleeding events as the primary endpoint to determine the efficacy of prophylactic treatment. As such, untreated bleeding episodes are often underreported. It is important to consider both treated and untreated bleeding events to understand overall bleed management. We describe the characteristics of treated and untreated bleeding events in the BASIS study.

Methods: BASIS enrolled male pts aged ≥12 to <75 years with severe HA or moderately severe to severe HB, with or without inhibitors. Results are reported for the non-inhibitor cohort; the inhibitor cohort is ongoing. Pts entered a 6-month observational phase (OP) and received their prescribed factor replacement therapy (OD or RP) before crossing over to the 12-month active treatment phase (ATP) to receive a single loading dose of 300 mg marstacimab (2x150 mg SC) followed by 150 mg SC QW. The incidence of bleeding episodes, including etiology (spontaneous, traumatic, or procedural), location (joint or soft tissue/muscle), and whether treatment was required (intravenous coagulation factor products or bypass agents) were obtained from pt diaries and medical records. Bleed data were collected over 6 months for the OP phase and 12 months for the ATP phase. Descriptive data are presented.

Results: In total, 128 pts (median age 30 [range 13-66] years) entered the 6-month OP (n: OD: HA 29, HB 8; RP: HA 72, HB 19) and 116 (n: OD 33, RP 83) continued to the 12-month ATP. At baseline, 89 (69.5%) pts (OD: n=36; RP: n=53) had ≥1 target joint. The mean (range) duration of marstacimab treatment was 12.1 (11.5-13.1) months for the OD group and 11.6 (0.9-12.8) months for RP group. Of 116 pts, 88 (75.9%; OD 33 [100%], RP 55 [66.3%]) experienced ≥1 bleeding event during the 6-month OP and 85 (73.3%; OD 29 [87.9%], RP 56 [67.5%]) during the 12-month ATP. The total number of bleeding events during the 6-month OP was 1312 (n: OD 899 [68.5%]; RP 413 [31.5%]), of which 1114 (84.9%) were treated (OD 83.3%; RP 88.4%). The total number of bleeding events during the 12-month ATP was 687 (n: OD 243 [35.4%]; RP 444 [64.6%]), of which 504 (73.4%) were treated (OD 48.6%; RP 86.9%). The majority of bleeding episodes were spontaneous in both the OD (OP 83.4%; ATP 77.4%) and RP (OP 72.4%; ATP 70.5%) groups. In both groups, most bleeds occurred in joints (OP: OD 84.0%, RP 62.5%; ATP: OD 82.3%, RP 71.6%) than in soft tissue/muscle (OP: OD 13.0%, RP 32.2%; ATP: OD 13.2%, RP 25.9%). The most common sites of joint bleeds were the ankle/foot, elbow, and knee for both groups in the OP and ATP.

Conclusions: The majority of bleeds across both OD and RP groups during the BASIS study (OP and ATP) were spontaneous, treated, and occurred in joints, most commonly the ankle/foot, elbow, and knee. In the OD group, marstacimab prophylaxis resulted in a greater proportion of pts without any bleeding events and a lower proportion with treated bleeds during the ATP vs the OP. Of pts who had bleeding events, the RP group had a relatively greater proportion of treated bleeds (86.9%) vs the OD group (48.6%). Of note, in pts with prior FVIII prophylaxis in the HAVEN-3 emicizumab study who had bleeds, 24% of total bleeds were treated (Callaghan et al, RPTH, 2022), suggesting differences in bleed management vs the BASIS study. Overall, these results demonstrate that a high proportion of bleeding events were treated with factor replacement therapy in the BASIS study, but that clinical management and treatment strategies may differ across trials.

A Fixed (Weight-independent) Subcutaneous Once-Weekly Dose for Marstacimab, an Anti-TFPI Monoclonal Antibody for the Prophylactic Treatment of Hemophilia A and B (ASH 2024)

S. Nayak et al

Introduction: Marstacimab is a human anti-TFPI monoclonal antibody currently in phase 3 development, intended for routine prophylaxis treatment to prevent or reduce the frequency of bleeding episodes in hemophilia A or B patients (with or without inhibitors). Marstacimab demonstrated superiority over routine prophylaxis treatment and superiority over on-demand treatment as measured by Annualized Bleed Rate (ABR) of treated bleeds in the phase 3 study (EAHAD 2024 abstract # 285). A once-weekly weight independent (i.e. flat/fixed), subcutaneous dosing regimen for marstacimab is expected to provide significant advantages of patient convenience, compliance, less risk of dosing errors and cost-effectiveness over current standard of care.

Methods: Data from hemophilia participants receiving once weekly (QW) marstacimab at doses of 150 mg subcutaneous (SC) QW (with a loading dose of 300 mg SC), 300 mg SC QW and 450 mg SC QW in Phase 2 (NCT03363321, NCT02974855) and phase 3 (NCT03938792) studies were included in the analysis. To understand the effect of weight on marstacimab PK and PD ie. peak thrombin (biomarker closely related to clinical bleed endpoint; Verhagen et al, 2023), 5000 PK and PD simulations were performed for a uniform weight distribution in the range of 30 to 120 kg (~500 subjects in each 10-kg weight category). Simulations were performed using R (ver. 4.2.1) and were based on a population PK model using Target Mediated Drug Disposition (for PK) and an E_{max} model (for PD) model with model parameters estimated in NONMEM (v 7.5.0). Steady-state average, maximum and minimum drug concentration and peak thrombin values were calculated for each participant.

Results: PK: Simulated marstacimab concentrations were seen to decrease with increasing weights (weight range: 35 – 74 kg for adolescents and 43 – 120 kg for adults). Marstacimab exposures ($C_{avg,ss}$, $C_{max,ss}$ and $C_{min,ss}$) were calculated to be approximately 2 to 2.5-fold higher in adolescents compared to adults. In general, an overlap was seen for the observed concentration range across the 40 – 50 kg to 80 - 90 kg weight categories. PK simulations showed that median $C_{avg,ss}$ exposures are predicted to be ~ 4X higher for the 30 - 50 kg group and ~ 6X lower for the 100 - 130 kg group in comparison to predicted exposures for a standard weight of 70 - 80 kg. At lower weights, the higher concentrations are predicted to be below the maximum concentrations seen in clinical studies (Maximum Tolerated Dose i.e MTD not reached). At higher weights, concentrations are predicted to be above the marstacimab plasma EC_{50} based on animal and phase 1/2 clinical data. **PD:** No trends in peak thrombin are seen based on weight; median and range of peak thrombin values are comparable across all weight categories. Furthermore, peak thrombin values are generally within the normal physiological range without evidence of any excessive pharmacology (ISTH 2024 poster # PB0518). This trend is likely explained by marstacimab concentrations being in the maximal effect range of the exposure-response relationship. **ABR:** No apparent trends are seen in the median ABR values across the weight categories. To date, no thromboembolic events have been observed in hemophilia patients at any of the clinical doses (EAHAD 2024 poster # P0186).

Conclusions: A flat (fixed) dosing regimen for marstacimab, supported by comparable PD and ABRs across weight ranges, lack of safety concerns to date and an absence of a narrow therapeutic window profile, provides significant advantages of patient convenience, compliance, less risk of dosing errors as well as cost-effectiveness.

Von Willebrand Disease and Other Rare Bleeding Disorders

Delivering Transcutaneous Auricular Neurostimulation to Reduce Heavy Menstrual Bleeding in Von Willebrand Disease Patients (ASH 2024)

C J Czura et al

Background: Heavy menstrual bleeding (HMB) is defined as excessive blood loss that interferes with women's quality of life. HMB can be accompanied by other symptoms including dysmenorrhea, headache, fatigue, and anemia. About 10-15% of women with HMB have an underlying bleeding disorder, while 75-100% of women with von Willebrand Disease (VWD) experience HMB. While strategies including hormone therapy, desmopressin, recombinant factor, and hysterectomy demonstrate clinical benefit, HMB+VWD patients continue to experience poorer quality of life and greater healthcare resource utilization that general populations.

Transcutaneous auricular neurostimulation (tAN) is an FDA-cleared technology (Sparrow Ascent System, K230796) that stimulates branches of the vagus and trigeminal nerves on and around the ear. This technology leverages decades of clinical application of implantable cervical vagus nerve stimulation (VNS), which is an accepted therapy for the treatment of refractory epilepsy, depression and stroke. Studies show that cervical VNS also reduces bleeding times and shed blood volumes in animal models of soft tissue injury by rendering platelets more responsive to pro-coagulant stimuli. This approach was also effective in mice deficient in Factor VIII, suggesting that VNS may be a novel tool in the management of bleeding disorders. Transcutaneous auricular neurostimulation is an emerging non-invasive alternative to cervical VNS and has been applied for headache, migraine, heart failure, asthma, tinnitus, and other conditions . tAN stimulates the release of central nervous system endorphins, shifts circulating monocytes to an anti-inflammatory phenotype , inhibits pro-inflammatory cytokine release, and has sustained antinociceptive effects. tAN is currently being tested in a healthy human population to determine whether it can alter platelet phenotype.

Study design and Treatment: This open-label, decentralized pilot study will study whether tAN can reduce menstrual blood loss and improve health-related quality of life and menstrual symptoms in 10 VWD Type 1 participants with HMB when applied during menstruation. Participants will be enrolled in the study over the course of two consecutive menstrual cycles. During the Baseline Menstruation, no tAN treatment will be delivered, and Participants will estimate daily blood loss using a validated pictorial blood loss assessment chart (PBAC). Dysmenorrhea, quality of life, and duration of menstruation will be collected on the final day of the baseline menstruation using the Cox Menstrual Symptom Scale (CMSS), the Short Form (SF)-36, and the PBAC. During the Second Menstruation, participants will self-administer two daily 1-hour sessions of active tAN beginning Day 1 through the final day of Second Menstruation. Participants will estimate daily blood loss with the PBAC throughout the duration of their second menstruation, and the CMSS and SF-36 will be collected on the final day.

Eligibility Criteria: Inclusion criteria are regularly menstruating female participants between 18-45 years of age; diagnosis of VWD Type 1; history of menorrhagia as assessed by the Menorrhagia Screening Tool; on oral birth control (≥ 3 months) and willing to continue use throughout the study.

Exclusion criteria are antifibrinolytic use within 30 days of enrollment; acquired bleeding disorder; use of anticoagulants including platelet inhibitors for 30 days prior to enrollment; known structural cause of HMB.

Statistical Methods: Mean total PBAC, CMSS and SF-36 scores will be compared between menstruations using the paired Student's T test. Average areas under the curve of daily PBAC scores will be computed for the baseline and treatment menstruations and compared with standard error and confidence intervals using Graphpad Prism.

A Phase Ia Study of VGA039, a Protein S-Targeting Monoclonal Antibody, in Individuals with Von Willebrand Disease Demonstrates Concentration-Dependent Increases in Thrombin Generation for Reducing Bleeding (ASH 2024)

C M Millar et al

Introduction: Non-factor replacement therapies have the potential to provide hemostatic 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 disorders, including von Willebrand disease (VWD), and prevent blood loss in vivo in a novel, non-human primate (NHP) VWD model. In healthy volunteers (HVs), single ascending doses (SADs) of subcutaneous (SC) VGA039 increase thrombin generation in a dose- and concentration-dependent manner (Schörgenhofer et al., ISTH 2024). The objective of this SAD study is to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of SC VGA039 in VWD patients.

Methods: This is an open-label phase Ia study (NCT05776069) conducted in adult individuals with VWD and approved by local ethics committees. Informed consent was obtained. Key eligibility criteria included: (1) symptomatic VWD of any type or subtype, (2) baseline FVIII activity level ≤50 IU/dL, (3) and no laboratory evidence of thrombophilia or prior history of thromboembolism. The starting SC SAD of 3.0 mg/kg was the pre-specified maximum dose tested in HVs and selected as the initial SAD to be tested in individuals with VWD. Continued dose escalations in subsequent cohorts were determined based on emerging D-dimer levels, with a dose limiting toxicity (DLT) threshold set at 4 times the upper limit of normal.

Results: As of August 1, 2024, a total of 6 subjects equally divided into 2 SAD cohorts (3.0 and 4.5 mg/kg) have been dosed: 1 with Type 1 VWD + mild hemophilia A, 1 with Type 2A VWD, 2 with Type 2M VWD, and 2 with Type 3 VWD. Related to VGA039, there were no adverse events, changes in coagulation laboratory parameters, thromboembolic events, DLTs, or injection-site reactions that have been reported. While mild increases in D-dimer levels were observed in healthy volunteers at 3.0 mg/kg, no significant D-dimer elevations have been observed in VWD subjects at either 3.0 or 4.5 mg/kg. Preliminary thrombin generation results show increased thrombin generation at similar VGA039 concentrations in VWD subjects as in HVs. Additional clinical, PK, and PD data for these and subsequent SAD cohort(s) will be presented at the meeting.

Conclusions: Clinical data suggest VGA039 is well tolerated and can increase thrombin generation in the absence of clinically significant D-dimer elevations in individuals with VWD. Drug concentration data continue to support the potential for weekly or less frequent SC prophylactic dosing. Further

SAD evaluation of VGA039 in VWD patients is ongoing, and future multi-dose and surgical prophylaxis 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

RE-BALANCING 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 Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Concizumab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Novo Nordisk	Phase 3 (approved for PHABwI in Canada, Australia, Japan and EU)
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Marstacimab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Pfizer	Approved by EMA
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

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GENE THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Gene Therapy	Haemophilia A	PF-07055480 giroctocogene fitelparvovec (formerly SB-525)	Gene therapy using a rAAV2/6 vector, encoding the B-domain deleted human FVIII	Single intravenous infusion	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	Single intravenous infusion	Expression Therapeutics	Phase 1

			haematopoietic stem cells and lentiviral vectors			
Gene Therapy	Haemophilia A for HAwI	SPK-8016	Recombinant AAV composed of a liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette	Single intravenous infusion	Spark	Trial suspended
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	Single intravenous infusion	Christian Medical	Phase 1

			(encoding human factor VIII gene) is administered by IV infusion following conditioning regimen		College, Vellore, India	
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 Innovators' Open Technology Programme, Project#18712	Pre-clinical phase

CELL-BASED THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	Haemophilia A with inhibitors	TI-168	Autologous FVIII TCR-Treg cell therapy	-	TeraImmune Inc.	Phase 1/2a clinical trial planned for 2024, Orphan drug status granted by FDA
Cell-based therapy	Haemophilia B	BE-101	Engineered B Cell medicine	Single infusion	Be Biopharma	Launch of Phase 1/2 trial (BeCoMe-9) in late 2024

LICENSED FACTOR REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	VWD	Veyvondi® Vonvendi®	rVWF (vonicog alfa)	Takeda	Licensed
Replacement VWF 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-human FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	Licensed
Replacement FVIII	Haemophilia A	Refacto AF®	Moroctocog alfa	Pfizer	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 FXIII	Factor XIII deficiency	NovoThirteen®/ Tretten	Recombinant FXIII (catridecacog)	Novo Nordisk	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

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	Approved by EMA in July 2024, brand name Durveqtix, also approved by FDA and Health Canada as Beqvez