NOVEL TREATMENTS IN HAEMOPHILIA & OTHER BLEEDING DISORDERS: A PERIODIC REVIEW 2024 - ISSUE 2

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Contents

Forward

Welcome to the second edition for 2024 of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia, von Willebrand disease and other rare bleeding disorders.

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

Note that bypassing agents and rebalancing therapies have been given their own categories separate from specific bleeding disorders as they may be of use across multiple conditions.

This publication covers developments in coagulation products that are in clinical trials, that have recently received marketing approvals or whose indications are being expanded, but does not delve into the basic science of rare bleeding disorders and their treatments. To obtain this type of information, we would suggest consulting the EHCucate app (available on iOS and Google Play), which provides basic scientific concepts on rare bleeding disorders and the mechanisms of action of their treatments, and the World Federation of Hemophilia education and e-learning section (https://wfh.org/education-and-elearning/).

In this edition, we primarily cover advances presented at the European Association for Haemophilia and Allied Disorders (EAHAD) Congress held in February 2024, the World Federation of Hemophilia (WFH) Congress held in April 2024 and the International Society of Thrombosis and Haemostasis Congress (ISTH) held in June 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 January 1, 2024.

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

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

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- Dr Maria Elisa Mancuso, EHC volunteer
- Asst Prof Brian O'Mahony, EHC volunteer
- Prof Johannes Oldenburg, EHC volunteer
- Mr David Page, Canadian Haemophilia Society
- Dr Suthesh Sivapalaratnam, EHC Volunteer
- 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,

Brian O'Mahony, IHS Chief Executive Miguel Crato, EHC President

Abbreviations

> Greater than
≥ Greater or equal to
< Less than
≤ Less than or equal to
Ab Antibodies
AAV Adeno-associated virus
ABR Annualised bleeding rate
ADAs Anti-drug antibodies
AE Adverse events
AFP Alphafetoprotein
ALT Alanine transaminase
AjBR Annualised joint bleeding rate
AsBR Annualised spontaneous bleeding rate
ASH American Society of Hematology
aPCC Activated prothrombin complex
aPTT Activated partial thromboplastin time
AST Aspartate transaminase
AT Antithrombin
ATHN American Thrombosis and Hemostasis Network
AUCinf Area under the curve extrapolated to infinity
BDD B-domain deleted
BE Bleeding episode
BLA Biologics License Application
BP Bodily pain / Blood pressure
BPA Bypassing agents
BU/ml Bethesda units per millilitre
CFB Change from baseline
CFC Clotting factor concentrates
CHMP Committee for Human Medicinal Products
CI Cumulative incidence
CI Confidence interval
CID Clinically important difference
CL Clearance
Cmax The peak plasma concentration after drug administration.
CSA Chromogenic substrate assay
CV Cardiovascular
CVAD Central venous access device
CWA Clot waveform activity
DNA Deoxyribonucleic acid
DMC Data Monitoring Committee
DVT Deep vein thrombosis
EAHAD European Association for Haemophilia and Allied Disorders
EC European Commission
ECLA Electrochemiluminiscent
ED Exposure days
EHL Extended half-life
ELISA Enzyme-linked immunoassay
EMA European Medicines Agency
EQ-5D-5L Standardised measure of health-related quality of life
F Factor
FDA Food and Drug Administration
FVII Factor VII
FVIIa Factor VII activated
FVIID Factor VII deficiency
FVIII Factor VIII
FIX Factor IX
FX Factor X
gc/kg Genome copies per kilogram
h Hours
HA Haemophilia A
Haem-A-QoL Haemophilia-Specific Quality of Life Questionnaire for Adults
HAL Haemophilia activity list
HAwI Haemophilia A with inhibitors
HB Haemophilia B
HBwI Haemophilia B with inhibitors
HCRU Healthcare resources utilisation
Hemo-TEM Haemophilia Treatment Experience Measure
HCV Hepatitis C virus
HIV Human immunodeficiency virus
HJHS Haemophilic joint health score
HMW High molecular weight
HRQoL Health-related quality of life
HTC Haemophilia treatment centre
HTI High titre inhibitors
IDR Initial dosing regimen
IND Investigational new drug
IR Incremental recovery
ITI Immune tolerance induction
IQR Interquartile range
ISTH International Society for Thrombosis and Haemostasis
IV Intravenous
IU International units
IU/dL International units per decilitre
IU/kg International units per kilograms
kg Kilogram
LTI Low-titre inhibitors
mg/kg Miligrams per kilograms
mg/kg/week Milligrams per kilograms per week
mHJH Modified haemophilia joint health score
mITT Modified intent to treat
MoA Mode of action
MOI Multiplicity of infection
n= Number
NAbs Neutralising antibodies
NATEM Non-activated thromboelastometry
ng/ml Nanogram per millilitre
OD On-demand

OSA One-stage assay
P Probability
Pd Plasma-derived
PD Pharmacodynamics
PE Pulmonary embolism
pedHAL Paediatric haemophilia activity list
PEG Polyethylene glycol
PF Physical function
PK Pharmacokinetics
PKP Pharmacokinetics-guided prophylaxis
PPX Prophylaxis
PROs Patient Reported Outcomes
psHA People with severe haemophilia A
PTP Previously treated patients
PUP Previously untreated patients
PwHA People with haemophilia A
PwHB People with haemophilia B
PwHAI People with haemophilia A and inhibitors
PwHBI People with haemophilia B and inhibitors
PwHBAI People with haemophilia A or B and inhibitors
Q&A Questions and answers
QM Every month
QW Once a week
R Recombinant
rFVIIa Recombinant factor VII activated
ROTEM Rotational thromboelastometry
RNA Ribonucleic Acid
RTP Return to prophylaxis
SAE Serious adverse event
SC Subcutaneous
s.c. Subcutaneous
SD Standard deviation
SHL Standard half-life
siRNA Silencing RNA
SP Standard prophylaxis
SQ Subcutaneous
T . Half-life
TE Thromboembolic events
TEAE Treatment emergent adverse events
TFPI Thrombin factor pathway inhibitor
TG Thrombin generation
TGA Thrombin generation assay
TMA Thrombotic microangiopathy
Tmax The time to reach Cmax
TSQM-9 Treatment satisfaction questionnaire for medication
ug/mL Micrograms per millilitre
ULN Upper limit normal
UK United Kingdom
UKHCDO United Kingdom Haemophilia Clinic Doctors' Organisation
US United States
vg/kg Vector genomes per kilogram
VAS score Visual analogue scale
vs Versus
VWD von Willebrand disease
VWF von Willebrand factor
W Week
WAPPS-Hemo Web Accessible Population Pharmacokinetic Service-Haemophilia
WFH World Federation of Haemophilia
WHO World Health Organisation
µg Microgram
µg/kg Microgram per Kilogram
µL Microlitre

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. Efanesoctocog alfa was approved by the U.S. and Japanese regulatory authorities in 2023. See pages 11, 23-26.

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

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 2024. See pages 10, 21-22.

Hoffmann-La Roche announced the start of a Phase I/II, open-label, non-randomized, global, multicenter, multiple-ascending dose (MAD) study in adult and adolescent male participants with severe or moderate haemophilia A with or without factor VIII (FVIII) inhibitors. to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity, and efficacy of multiple ascending doses of **NXT007**, a next-generation bispecific antibody that mimics the role of FVIII in the coagulation cascade.

In an oral communication at ISTH, Jacob Lund on pre-clinical work to develop **Inno-8**, the first ever oral FVIIIa mimetic treatment for haemophilia A. Inno-8 is a novel VHH-based FVIIIa-mimetic molecule with ultra-high potency to enable once-daily oral treatment of HA. The antigen-binding site of these unusual heavy chain antibodies is formed by a single domain, designated VHH in camelids. VHH is easily produced as recombinant proteins, designated single domain nanoantibodies or nanobodies and represent the smallest molecule in nature capable of binding a specific antigen. Inno8 was demonstrated to achieve similar in vitro activity as the sequence-identical analogue of emicizumab at approximately 90-fold lower concentrations. Moreover, Inno8 was shown to be orally available and exhibited a long systemic half-life of approximately 113 hours in beagle dogs. The Inno8 profile may thus allow for prophylactic once-daily oral treatment of HA. See page 22.

Hemab Therapeutics, a clinical-stage biotechnology company developing novel prophylactic therapeutics for serious, underserved bleeding and thrombotic disorders, presented Phase 1 data for **HMB-001**, a novel bispecific antibody, in Glanzmann Thrombasthenia (GT) at EAHAD in February 2024 and announced that Phase 2 will expand clinical trial sites across Europe and the United States. In addition, the US Food & Drug Administration (FDA) granted Fast Track designation to HMB-001, emphasizing the seriousness and high unmet need for treatments for GT. See pages 43-44.

tRNA-Based Protein Editing

hC Bioscience, a biopharmaceutical company developing a fundamentally novel approach to treating genetic diseases through tRNA-based protein editing, announced preclinical data supporting its lead program in severe haemophilia A at the World Federation of Haemophilia 2024 World Congress. It will build on these preclinical data with the goal of enrolling on a Phase 1 clinical trial for severe haemophilia A in 2025. **HCB-101** is an anticodon-engineered tRNA designed to suppress nonsense mutations. It is delivered as a lipid nanoparticle to target the liver. The data presented demonstrate successful targeting of the liver in mice as well as successful in vitro production of full-length, functional FVIII despite the presence of a premature termination codon (PTC) that would otherwise result in a truncated nonfunctional protein. This approach has the potential for application in about 20% of severe haemophilia A cases and could be extended across a broad spectrum of other diseases caused by nonsense mutations.

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), is still awaiting marketing authorisations from the EMA and the U.S. FDA. See pages 37-40.

Marstacimab, another anti-tissue-factor pathway inhibitor, is also awaiting decisions on marketing authorisations after submissions in 2023 for the prophylactic treatment of people with haemophilia A or B. See pages 40.

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 the end of March 2025. See pages 41-42.

Centessa Pharmaceuticals has initiated a pivotal trial in approximately 70 sites in 20 countries for **SerpinPC**, an investigational serine protease inhibitor engineered to inhibit Activated Protein C (APC) for the treatment of haemophilia A and B.

Gene therapy for haemophilia A

A phase 1/2 study (GENEr8-INH) on the safety and efficacy of **valoctocogene roxaparvovec (Roctavian)** in participants with active and prior FVIII inhibitors has started. Preliminary efficacy results from 4 patients are encouraging. See pages 11-12, and 26-29.

Spark Therapeutics / Roche reported that a Phase 3, single-arm, open-label, multicenter study of the safety and efficacy 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 is now recruiting. The purpose of this study is to evaluate the efficacy of SPK-8011 in preventing bleeding episodes compared with FVIII prophylaxis in participants with haemophilia A without FVIII inhibitors on routine FVIII prophylaxis. The primary completion date is 2027. See pages 12, and 28-29.

In July 2024, Pfizer reported results from its ongoing phase 3 trial of giroctocogene fitelparvovec (formerly SB-525). The company said its gene therapy for haemophilia A showed superiority compared to factor VIII replacement therapy in reducing the annual bleeding rate. Data from the 75 participants showed that 84% of patients who were given the gene therapy had FVIII levels above 5% at 15 months post-infusion. Pfizer is co-developing the haemophilia A gene therapy with Sangamo Therapeutics.

In a late-breaking abstract (LBA-FP-001) presented at WFH Congress, a phase 1 study led by A. Srivastava has begun to validate a gene therapy approach in haemophilia A with a novel FVIII transgene delivered through lentiviral vector transduced autologous CD34+ hematopoietic stem cells. Results from the first three trial participants show clinically sustained FVIII elevations and no major safety concerns.

Gene therapy for haemophilia B

In its final draft guidance in June 2024, the U.K.'s National Institute of Health and Care Excellence NICE) has recommended that **etranacogene dezaparvovec (Hemgenix)** gene therapy should be made available on the NHS as a treatment option for adults with moderately severe or severe haemophilia B, through managed access over a limited five-year period while further clinical evidence of its effectiveness is gathered. Hemgenix is approved by the EMA, U.S. FDA and Health Canada. Canada's Drug Agency (previously CADTH) also issued a positive reimbursement recommendation, conditional

on a price reduction, in March 2024. See pages 13, 30-33.

CSL Behring announced a Phase 4, observational, post-authorization, long-term follow-up, multicenter, international study (NCT06008938) investigating **etranacogene dezaparvovec (Hemgenix)** in adults with haemophilia B. Two cohorts (each targeting enrollment of n~250) will include patients with haemophilia B given either 1) commercially available etranacogene dezaparvovec as a single intravenous infusion, or 2) FIX prophylaxis while enrolled in the American Thrombosis and Hemostasis Network Transcends: Natural History Observational Cohort Study or in local registries in other countries. For both cohorts, patients will be enrolled 5 years from enrollment of the first patient treated post-approval (June 15, 2023) and followed for 15 years.

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. See pages 13, 33-35.

Regeneron is planning to begin by mid-year 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.

Be Biopharma plans to launch a Phase I/II study (BeCoMe-9) of **BE-101** in adults with haemophilia B in the second half of 2024. The US Food and Drug Administration (FDA) has granted orphan drug designation to BE-101 for the treatment of haemophilia B. BE-101 is a newly engineered B Cell medicine, designed to deliver the human FIX gene into primary human B cells with a single infusion, enabling the expression of active FIX to manage haemophilia B. See pages 35.

Transcutaneous auricular nerve stimulation

During a webinar presented by the National Bleeding Disorder Foundation in the U.S., Spark Biomedical announced the start of a 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.

2 - Report Highlights
An Update On Novel Therapies In Haemophilia A

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

Mim8

Efficacy and safety of Mim8 prophylaxis in adults and adolescents with haemophilia A with or without inhibitors: Phase 3, open-label, randomized, controlled FRONTIER2 study

In a late-breaking session (LB 01.5) at ISTH, Maria Elisa Mancuso et al reported Phase 3 results from the FRONTIER2 study. They concluded that the FRONTIER2 demonstrated the superiority of **Mim8** prophylaxis once-every-week and once-every-month in reducing ABR for treated bleeds compared with either on- demand treatment or clotting factor concentrate prophylaxis. Mim8 was well tolerated, and no safety concerns were observed. See pages 21.

FVIII In Vitro Bioequivalence of Mim8 Haemostatic Effect by Thrombin Generation Assays

https://isth2024.eventscribe.net/fsPopup.asp?efp=R0tKSkNBT0ExNjMzNg&PresentationID=1433378&rnd=0.4048342&mode=presInfo

In an oral communication session (OC 50.5) at ISTH, David Lillicrap et al estimated the FVIII in vitro bioequivalence of denecimig (**Mim8**) versus **emicizumab**. They concluded FVIII in vitro bioequivalence for Mim8 was 6.1–36.8% versus 4.7–16.4% for emiSIA, depending on assay conditions. Given the large span in estimated FVIII in vitro bioequivalence for both molecules, its translation to clinical efficacy is currently unknown. Mim8 had a higher thrombin peak in conditions with limited FIXa compared with emi-SIA, suggesting mode-of-action differences. See pages 21-22.

Emicizumab (brand name Hemlibra)

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

https://ashpublications.org/blood/article/143/14/1355/506683/Emicizumab-prophylaxis-in-infants- with-haemophilia

In a paper published in Blood in April 2024, Steven Pipe et al reported results from HAVEN 7, the first clinical trial of emicizumab dedicated to infants. They reported that 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. Researchers concluded that this primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors. See page 18.

Emicizumab prophylaxis in people with haemophilia A: Summary of 10 years of safety data on thromboembolic events and thrombotic microangiopathy

https://medically.roche.com/content/dam/pdmahub/restricted/haematology/eahad-2024/EAHAD-2024-poster-sarouei-emicizumab-prophylaxis-in-people-with-haemophilia.pdf

In a poster at EAHAD (PO126), K. Sarouei et al presented a summary of 10 years of safety data on thromboembolic

events (TE) and thrombotic microangiopathy (TMA) in people with haemophilia A on emicizumab prophylaxis. The poster analyses risk factors in the 155 total TE/TMA events in reports from 24 countries. Over 24,000 people have received post-marketing emicizumab as of mid-2023. They found that no new safety concerns were observed since the last data cut-off and the benefit-risk profile remains positive. Health authorities no longer require special expedited safety reporting of TE/TMAs for emicizumab; however, monitoring and reporting of safety data are ongoing, with no new safety signals with increased patient emicizumab exposure found to date. See pages 18-19.

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

In an oral communication (OC 50.2) at ISTH, Manuela Albisetti et al reported on 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. 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. See pages 23.

Gene Therapy

Valoctocogene roxaparvovec (brand name Roctavian)

Seven-year follow-up of valoctocogene roxaparvovec gene therapy for haemophilia A

Bella Madan et al

In an oral communication at ISTH, Madan et al provided an update on the seven-year follow-up of the phase 1/2 dose escalation trial of valoctocogene roxaparvovec gene therapy for haemophilia A. Six people received an infusion of 4x1013 vg/kg and seven people received 6x1013. Results include factor levels, changes I factor levels over time, ABs, infusion rates, details on returns to prophylaxis and treatment- related adverse events. See page 26-27.

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

In an oral communication (OC 30.2) at ISTH, Leavitt et al reported on 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 bleed control and FVIII expression were maintained 4 years post-valoctocogene roxaparvovec treatment. No new safety signals emerged. See pages 27.

Dirloctogene samoparvovec

Long-Term Follow-Up of Participants in the Phase I/II Trial of Dirloctocogene Samoparvovec (SPK-8011): Durable FVIII Expression and Clinically Meaningful Reduction of Bleeding

In an oral communication (OC 02.4) at ISTH, Stacy E. Croteau et al reported on the long-term safety and efficacy of **dirloctocogene samoparvovec (SPK-8011)** and novel non-steroid immune prophylaxis (tocilizumab, mycophenolate mofetil) use in the Phase I/II trial. 25 participants were enrolled. No FVIII inhibitors or thrombotic events occurred. FVIII expression was sustained in most participants. Three participants returned to prophylaxis. Median annualized bleed rate (ABR) post dirloctocogene samoparvovec administration was 0.2 (Q1–Q3: 0.0–3.2) vs historical ABR of 5.0 (1.0–11.0) on prior prophylaxis. Up to 7 years post dirloctocogene samoparvovec administration, data indicate that investigational gene therapy was well tolerated, with durable FVIII expression and clinically meaningful ABR reductions. Non-steroid immune prophylaxis did not abrogate use of steroids to treat presumed immune response. See pages 28-29.

Gene Therapy

Etranacogene dezaparvovec (Hemgenix)

Etranacogene dezaparvovec haemophilia B gene therapy phase 2b trial final results: stable and durable FIX level expression over 5 years

In an oral presentation (OC 02.3) at ISTH, Sandra le Quellec et al reported on a Phase 2b, open-label, multi- center trial (NCT03489291) in which 3 HB patients on routine prophylaxis received a single intravenous dose of **etranacogene dezaparvovec** (2×1013 gc/kg) and were followed for 5 years. All 3 participants had neutralizing antibodies (NAbs) to AAV5 at mean titer of 25 at dosing. Mean aPTT-based FIX activity remained stable throughout the trial duration: from Year 1 (40.7%) to Year 5 (46.7%). At Year 5 post-dose, FIX activity measured 46.8%, 39.0% and 51.2% in the 3 participants, respectively. Mean and median ABR for the cumulative follow-up period Years 0–5 was 0.14 and 0, respectively, for all bleeds. No patients returned to FIX prophylaxis. There were no treatment-related serious adverse events. See pages 31.

Fidanacogene elaparvovec (Durveqtix)

Efficacy and safety of fidanacogene elaparvovec in adults with moderately severe or severe haemophilia B: updated results from the phase 3 BENEGENE-2 gene therapy trial

In an oral presentation (OC 30.5) at ISTH, Kaan Kavakli et al reported on the BENEGENE-2 phase 3 trial of **fidanacogene elaparvovec (Durveqtix, Beqvez)** in participants with moderately severe or severe haemophilia B. As of August 2023, 44 participants completed ≥15 months follow-up (up to 4.0 years); the 45th participant had >12 months follow-up. Total ABR was reduced by 71% from Week 12 to Month 15 post-gene therapy vs prophylaxis. FIX activity remained stable at Month 24 in 39 participants. Twenty- eight (62%) participants received corticosteroids for presumed immune response. No deaths, infusion- related serious adverse events, thrombotic events, or FIX inhibitors were reported. See pages 33-34.

SS109

In an oral communication (OC 21.5) at ISTH, Mankai Ju et al reported results from an open-label, dose- escalation, multicenter phase I study to evaluate the safety, immunogenicity, and pharmacokinetics / pharmacodynamics（PK/PK) of single dose **SS109**, a long-acting rhFVIIa-Fc, in 27 haemophilia A/B patients with an inhibitor. The mean half-life ranged from 9.5 hours to14.5 hours, 3 to 7-fold longer than that of NovoSeven®. This study demonstrated that SS109 was well-tolerated and had dose-dependent PK/PD characteristics that support further assessment of its potential hemostasis efficacy in haemophilia patients with inhibitors.

TU7710

In a poster (PB0509) presented at ISTH, Byungwook Kim et al presented results on the TUB4PI-01 (NCT06025552) study to assess the pharmacokinetics (PK), pharmacodynamics (PD), and safety of single ascending doses of intravenous TU7710, a novel recombinant fusion protein linking activated FVII with human transferrin (rFVIIa-hTf), in warfarin pretreated healthy male subjects. TU7710 displayed prolonged half-life (12-13 hours) and successfully achieved normal INR levels in healthy subjects pre-treated with warfarin. This data provides support for the potential application of TU7710 in the treatment of haemophilia patients with inhibitors.

Concizumab (brand name Alhemo)

In an oral communication (OC 40.4) at ISTH, Anthony Chan et al presented efficacy results for **concizumab** (brand name **Alhemo**) at the 56-week cut-off in patients with haemophilia A/B without inhibitors: an intra- patient analysis from the phase 3 EXPLORER8 study. Concizumab is an anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibody, injected once daily, in development as a once-daily subcutaneous prophylaxis for patients with haemophilia A and B with and without inhibitors. For patients with HA, median ABR was 2.2 (0.8–6.2) on previous factor prophylaxis and 1.7 (0.5–4.8) on concizumab. For patients with HB, median ABR was 2.1 (0.9–4.2) on previous prophylaxis and 1.3 (0.0–6.4) on concizumab. Researchers concluded that low median ABRs for treated spontaneous and traumatic bleeding episodes were maintained at the 56-week cut-off, consistent with 32-week cut-off results, in patients with HA/HB without inhibitors, previously on stable factor prophylaxis. See pages 37-40.

Marstacimab

In a poster (POO74) at EAHAD, Johnny Mahlangu et al presented joint health outcomes in participants with haemophilia A and B without inhibitors treated with **marstacimab** from the phase 3 BASIS trial. Marstacimab is an investigational monoclonal antibody, injected subcutaneously once weekly, targeted to tissue factor pathway inhibitor (anti-TFPI) to improve haemostasis. Compared with on-demand (OD) treatment, **marstacimab** reduced the incidence of joint bleeds (32.9 vs. 2.8; $p < .0001$) and target joint bleeds (23.2 vs. 1.8; $p < .0001$). HJHS decreased 2.8 points versus OD ($p = .3$) at 6 months. Mean number of target joints were lower versus OD (0.2 [0.7] vs. 1.7 [1.4]). Compared with routine prophylaxis (RP), marstacimab reduced the incidence of joint bleeds (5.7 vs. 4.1, $p = .1680$) and target joint bleeds (3.4 vs. 2.5; $p = .2811$). HJHS decreased 2.0 points versus RP ($p = .0835$) at 6 months. Mean number of target joints were similar versus RP (0.3 [0.9] vs. 0.3 [0.7]). Researchers concluded that marstacimab reduced joint bleeds, HJHS and the number of target joints in patients with severe HA or moderately severe to severe HB without inhibitors and with high baseline prevalence of target joints versus prior OD or RP. Efficacy of marstacimab was maintained up to 16 months in the long-term extension study. See pages 40.

Fitusiran

In an oral communication (OC 40.2) at ISTH, Guy Young et al presented results on the **incidence of thrombotic events** in the **fitusiran** clinical development program. Analysis included 286 patients on the antithrombin-based dose regimen (AT-DR), targeting AT levels between 15–35%, and 270 exposed to the original dose regimen (ODR). There were nine thrombotic events reported in seven participants with the ODR, and four events in four participants with the AT-DR. Overall, only one thrombotic event, with the ODR, did not have any provoking or significant predisposing risk factors. The exposure-adjusted incidence rate of thrombotic events per 100 patient years was numerically lower with the AT-DR (0.82) versus the ODR (2.28). The researchers concluded that fitusiran antithrombin-based dose regimen mitigated the risk of thrombotic events in PwH A or B, irrespective of inhibitor status, compared with the original dose regimen. See pages 41-42.

In another oral communication at ISTH, Steven Pipe et al described **hepatobiliary events** in participants who received the fitusiran AT-DR (antithrombin-based dose regimen). Overall, 286 participants were included in the analysis, with total patient-years of exposure of 486.0. A total of 8/286 (2.8%) and 6/286 (2.1%) participants experienced ALT or AST elevations >3x upper limit of normal. All initial ALT/AST elevations >3xULN resolved spontaneously; mean (SD) time to resolution was 55 (26.3) and 45 (11.2) days. One event of asymptomatic transaminase elevation resulted in fitusiran discontinuation at physician discretion. There were no cases of severe liver toxicity or liver failure. Overall, 11/286 (3.8%) participants experienced events of cholecystitis/cholelithiasis, and one participant underwent cholecystectomy.

No events of cholecystitis/cholelithiasis resulted in discontinuation of fitusiran. The researchers concluded that liver transaminase elevations were infrequent and transient with the fitusiran AT-DR. Events of cholecystitis/cholelithiasis resolved without clinical sequalae and participants continued dosing with fitusiran. The pathophysiological mechanism for these events requires further elucidation and is under investigation. See page 42.

SerpinPC

In a late-breaking abstract (LBA-FP-003) presented at WFH, Trevor Baglin et al presented results from the AP-0101 study of **SerpinPC**, an investigational serine protease inhibitor engineered to inhibit Activated Protein C (APC). At a prophylactic dose of 1.2 mg/kg injected subcutaneously every 2 weeks, the mean ABR was reduced by 96% in severe haemophilia patients with a median ABR of 1.0. There were no treatment-related adverse events and no dose-dependent increases in D-dimer. Anti-drug antibodies were infrequent and did not affect steady-state **SerpinPC** levels.

An Update On Novel Therapies In Von Willebrand Disease And Other Rare Bleeding Disorders

VGA039

In an oral communication (OC 73.3) at ISTH, Christian Schoergenhofer 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 emerging data suggest VGA039 is well tolerated and increases thrombin generation in healthy volunteers. Drug concentration profiles demonstrate suitability for weekly or less frequent SC prophylactic dosing for various bleeding disorders. Further investigation of VGA039 is underway in VWD patients. See pages 43.

HMB-001

In an oral presentation (OR01) at EAHAD, S. Sivapalaratnam presented results of the first-in-human investigation of **HMB-001** for prophylactic management of glanzmann thrombasthenia (GT). HMB-001 is a bispecific antibody being developed by Hemab Therapeutics to prevent or reduce the frequency of bleeding episodes in patients with GT. HMB-001 works by binding to a membrane protein and accumulating endogenous activated coagulation factor VII (FVIIa) and targeting it to the surface of activated platelets at the site of vascular injury. This increases the activity of FVIIa to levels that are therapeutically effective. Participants in part A of the phase 1/2 study received HMB-001 subcutaneously at dose levels of 0.2 mg/kg, 0.5 mg/kg or 1.25 mg/kg, respectively. At the time of the abstract submission, there were no reported treatment-related adverse events. Pharmacodynamic data showed positive proof of mechanism with a dose-dependent increase in FVII and FVIIa as well as signs of coagulation activation based on a dose-dependent reduction in prothrombin time. The pharmacokinetic profile indicates a dose- dependent response and is supportive of infrequent, subcutaneous dosing. Researchers concluded that the initial safety, tolerability, pharmacodynamics and pharmacokinetics results from part A, a single ascending dose, of the phase 1/2 study are encouraging and support the further development of HMB- 001 as a potential prophylactic treatment for GT. See pages 43-44.

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

Steven Pipe et al

https://ashpublications.org/blood/article/143/14/1355/506683/Emicizumab-prophylaxis-in-infants-with-haemophilia

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.

Emicizumab prophylaxis in people with haemophilia A: Summary of 10 years of safety data on thromboembolic events and thrombotic microangiopathy (PO126, EAHAD 2024)

K. Sarouei et al

Introduction: The HAVEN 1 Phase 3 trial outlined thromboembolic events (TEs) and thrombotic microangiopathies (TMAs) as risks in people with congenital haemophilia A (PwcHA) when taking emicizumab with activated prothrombin complex concentrate (aPCC) at >100 U/kg/24 h for ≥24 h. We report updated safety data on emicizumab prophylaxis in PwcHA, as >24,000 people have now received post-market emicizumab (as of 18 July 2023; Roche, data on file).

Methods: Emicizumab safety reports from clinical trials, registries, expanded access, compassionate use and spontaneous post-marketing reports were analysed for TEs/TMAs. TEs were identified using the Medical Dictionary for Regulatory Activities (MedDRA v26.0) search strategy: 'Embolic and Thrombotic Events' Standardised Medical Query (Broad). TMAs were defined as MedDRA preferred terms: haemolytic uremic syndrome, microangiopathic haemolytic anaemia, microangiopathy, TMA, thrombotic thrombocytopenic purpura and renal-limited TMA.

Results: As of 1 August 2023, 155 total events meeting TE/TMA criteria were found from 24 countries in the Roche Global Safety Database; 97 were in PwcHA, including 34 since the previous analysis (15 May 2022). Two TEs and the five TMAs were related to aPCC (>100 U/kg/24 h for ≥24 h); 90 TEs were not. The new TMA since last analysis was due

to aPCC exceeding dose guidelines to treat diverticular haemorrhage in a patient with severe HA who then recovered. In 81 non-aPCC- and non-device-related TEs, median (range) age at event was 48 (0.8−84) years; 55 (67.9%) TEs were related to ≥1 cardiovascular/thrombosis- related risk factor and 26 (32.1%) reported insufficient information. Eleven (13.6%) of the 81 TEs and two (40%) of the five TMAs led to emicizumab discontinuation. Five (6.2%) TEs were fatal: two myocardial infarctions and one cerebrovascular event in three people with multiple risk factors, and two disseminated intravascular coagulation events related to pneumonia in two people >70 years old.

Discussion/Conclusion: No new safety concerns were observed since the last data cut-off and the benefit– risk profile remains positive. Health authorities no longer require special expedited safety reporting of TE/TMAs for emicizumab; however, monitoring and reporting of safety data are ongoing, with no new safety signals with increased patient emicizumab exposure found to date.

Cardiovascular safety and brain protective effect of emicizumab in patients with haemophila older than 40 (PO031, EAHAD 2024)

C. Hermans et al

Introduction: Frequent concerns have arisen regarding the cardiovascular safety and thrombosis risk in older patients with haemophilia, particularly those who have pre-existing cardiovascular risk factors (CRVF) on emicizumab. However, these concerns are predominantly grounded in limited real-world data.

Methods: To bridge this knowledge gap, we aimed to assess our proactive approach in adopting emicizumab across all our patients with severe haemophilia A, including older individuals with multiple comorbidities and CVRF.

Results: Out of the 117 patients with severe to moderately severe haemophilia A followed at the Saint- Luc University Hospital in Brussels, 52 are aged 40 or older. In the past three years, 44 (84%) patients opted to transition to emicizumab, while 8 (16%) chose to continue their prophylactic treatment with FVIII concentrate (standard half-life [3] and extended half-life FVIII [5]). Prior to switching to emicizumab, 34 patients were receiving FVIII prophylaxis, and 10 were on an on-demand treatment regimen. A majority of patients (42) now receive emicizumab every 4 weeks. Among them, 16 were observed to have an equivalent FVIII activity at a steady state, measured by chromogenic assay, exceeding 20%. Five patients did not have any known CVRF, while 19 had at least two CVRF, distributed as follows: hypertension (22), diabetes (5), high cholesterol (12), HIV treatment (7), obesity (7) and active smoking (15). One patient had atrial fibrillation (AF), and another had ischemic heart disease with a cardiac stent requiring platelet inhibition with clopidogrel at the initiation of emicizumab. Notably, during the follow-up period after the commencement of emicizumab, no cardiovascular events were observed, even in a patient aged 82 with AF and FV Leiden, who required hospitalisation for severe COVID-19 infection. In contrast, two patients on FVIII prophylaxis experienced intracranial bleeding due to uncontrolled hypertension, which was fatal in one case.

Discussion/Conclusion: Our experience, characterised by a lack of selection bias, does not substantiate the assumption that emicizumab is linked to an increased incidence of thrombotic events in older patients with multiple CVRF. Instead, our series suggests that emicizumab may have a significant protective effect against the incidence of intracranial bleeding, although confirmation in larger-scale studies is warranted.

Emicizumab in people with moderate or mild haemophilia an aged ≥40 years, with and without comorbidities (PO122, EAHAD 2024)

V. Jiménez-Yuste et al

Introduction: Few data exist on older people with haemophilia A (PwHA), particularly those with comorbidities. We present a post hoc analysis of people with non-severe HA aged ≥40 years from the HAVEN 6 trial (NCT04158648).

Methods: HAVEN 6 is a Phase 3 trial in people with moderate/mild HA without FVIII inhibitors, warranting prophylaxis (investigator-assessed; Negrier, Lancet Haematol 2023). Emicizumab was given at one of the three approved doses. An age cutoff of ≥40 years was selected for this exploratory analysis to obtain an older population with comorbidities, including cardiovascular (CV) risk factors (history of CV disease, hypertension, hyperlipidaemia, diabetes, body mass index ≥30 kg/m2), human immunodeficiency virus (HIV) and current or historical hepatitis C virus (HCV).

Results: At data cut-off (30 October 2021), 72 participants had been treated in HAVEN 6; 16 were aged ≥40 years and included in this analysis. Median (range) age was 50.5 (41−71) years, and all were male. Ten (62.5%) participants had moderate HA and 6 (37.5%) had mild HA. Nine (56.3%) participants had ≥1 CV risk factor, with 5 (31.3%) having ≥2. Three (18.8%) individuals had HCV only, 1 (6.3%) had HIV only, and 2 (12.5%) had HCV/HIV co-infection. Median (range) duration of emicizumab exposure was 1.1 (0.6−1.7) years. Fifteen (93.8%) participants had ≥1 adverse event (AE) and 3 (18.8%) had a serious AE, all unrelated to emicizumab. There were no fatal AEs, AEs leading to treatment withdrawal/modification/interruption, or thrombotic microangiopathies. One individual (with no CV risk factors or HIV/HCV infection) had a thromboembolic event (thrombosed haemorrhoid), unrelated to emicizumab. Three participants experienced a total of six treatment-related AEs: three injection-site reactions and one case each of fatigue, head discomfort and accidental overdose. The mean (95% confidence interval) ABR for treated bleeds for the 16 participants aged ≥40 years was 1.03 (0.03, 5.62), similar to that for the overall population of HAVEN 6 (0.94 [0.02, 5.48]). Eleven (68.8%) participants had zero bleeds, compared with 66.7% of the total population.

Discussion/Conclusion: The small population of people with moderate/mild HA aged ≥40 years precludes drawing firm conclusions from this analysis; however, the safety and efficacy of emicizumab did not differ notably from those observed overall in HAVEN 6

Low-dose emicizumab prophylaxis in patients with severe haemophilia A: a retrospective study bringing new hope for our patients (Journal of Thrombosis and Haemostasis, Volume 22, Issue 4, April 2024)

Rucha Patil et al

https://www.sciencedirect.com/science/article/pii/S153878362300925X

Background: Low-dose emicizumab can potentially offer a cost-effective treatment option in persons with haemophilia A, especially in developing countries.

Objectives: To compare the efficacy and safety of low-dose emicizumab with those on low-dose factor (F)VIII prophylaxis via chart review.

Methods: After ethics approval, chart data of 2 groups of patients were reviewed: group 1 (low-dose emicizumab, n = 10; 3 mg/kg monthly without a loading dose) and group 2 (low-dose FVIII prophylaxis, n = 10; 10-20 IU/kg of FVIII concentrates twice a week). Outcomes were target joints, annual bleeding rate, annual joint bleeding rate, Haemophilia Joint Health Score, nonactivated thromboelastometry–rotational thromboelastomety, clotting time, plasma emicizumab levels, and direct costs of treatment.

Results: All outcome measures were significantly better in the low-dose emicizumab group than in the low-dose FVIII prophylaxis group. For nonactivated thromboelastometry–rotational thromboelastometry, median values after 6 months in the low-dose emicizumab group were comparable with values seen patients with mild haemophilia, while the values in the low-dose FVIII prophylaxis group were similar to those of patients with moderate haemophilia. The direct cost of low-dose emicizumab was found to be approximately US $6000 and that for low-dose recombinant FVIII prophylaxis used in our study was US $6282 (the cost may range from US $3432 to $7920 depending on the type of factor) when compared to approximately US $15 000 for standard-dose emicizumab.

Conclusion: Low-dose emicizumab offers a cost-effective treatment option and can improve access in developing

countries. These findings need to be confirmed in a larger and better-controlled study.

Mim8

Efficacy and safety of Mim8 prophylaxis in adults and adolescents with haemophilia A with or without inhibitors: Phase 3, open-label, randomized, controlled FRONTIER2 study (LB 01.5, ISTH 2024)

Maria Elisa Mancuso et al

Background: Mim8 (denecimig) is a factor VIIIa mimetic bispecific antibody in clinical development for subcutaneous prophylaxis in haemophilia A (HA).

Aims: Evaluate the efficacy and safety of Mim8 in males and females (aged ≥12 years) with HA with or without inhibitors.

Methods: FRONTIER2 (NCT05053139) is a phase 3, open-label, randomized, controlled study. Mim8 was administered using tiered dosing (Figure 1). Primary objectives: demonstrate the hemostatic effect of Mim8 once-every-week (QW) and once-every-month (QM) at week 26 versus either on-demand treatment, or versus previous clotting factor concentrate (CFC) prophylaxis during the run-in period. Annualized bleeding rate (ABR) was estimated using a negative binomial regression model. Safety and immunogenicity were evaluated. Study was conducted following informed consent and ethical approval.

Results: Overall, 254 patients were randomized (Table 1). In patients previously treated on-demand, estimated mean ABR [95% CI] for treated bleeds was 0.45 [0.18;1.14] for QW and 0.20 [0.06;0.72] for QM Mim8 prophylaxis, versus 15.75 [10.7;23.2] for continued on-demand treatment (Table 1). Mim8 prophylaxis was superior to on-demand treatment, with ABR reduction of 97.1% (QW) and 98.7% (QM).

In patients on pre-study CFC prophylaxis, estimated mean ABR for treated bleeds was 2.51 [1.42;4.42] for QW and 1.78 [1.17;2.71] for QM Mim8 prophylaxis, versus 4.83 [3.59;6.51] and 3.10 [2.23;4.29], during run-in CFC prophylaxis, respectively (Table 1). Mim8 prophylaxis was superior to run-in CFC prophylaxis, with ABR reduction of 48.0% (QW) and 42.6% (QM).

Zero bleeds were observed in 65.3–95.0% of patients treated with Mim8 (Table 1). Injection-site reactions occurred in 5.0–12.2% of patients. There were no safety concerns and no clinical evidence of neutralizing anti-Mim8 antibodies.

Conclusion(s): FRONTIER2 demonstrated superiority of Mim8 prophylaxis once-every-week and once- every-month in reducing ABR for treated bleeds compared with either on-demand treatment or clotting factor concentrate prophylaxis. Mim8 was well tolerated, and no safety concerns were observed.

FVIII In Vitro Bioequivalence of Mim8 Haemostatic Effect by Thrombin Generation Assays (OC 50.5, ISTH 2024)

David Lillicrap et al

Background: Mim8 (denecimig) is a novel bispecific antibody mimicking activated factor VIII (FVIIIa), developed for subcutaneous prophylaxis treatment of haemophilia A with/without inhibitors. Whereas FVIII substitution therapy results in peak and trough FVIII levels, Mim8 provides steady-state exposure, allowing maintenance of high plasma activity level. Translation of Mim8 exposure to FVIII in vitro bioequivalence may add to the understanding of prophylactic coverage. Although both FVIII substitution therapy and Mim8 support thrombin generation (TG), their mechanisms of action (MoAs) are different, complicating the comparison. We used TG assays (TGAs) in plasma to predict FVIII in vitro bioequivalence of Mim8 and a sequence-identical analogue of emicizumab (emi-SIA).

Aims: To estimate FVIII in vitro bioequivalence of Mim8 and emi-SIA with TGA under multiple assay conditions.

Methods: TG in platelet-poor plasma from a congenital severe haemophilia A pool, supplemented with FVIII, 5 µg/mL Mim8 (clinically relevant concentration), or 50 µg/mL emi-SIA. TG was initiated with different triggers (tissue factor [TF], activated coagulation factor XI, or combinations thereof) to capture differences in MoA.

Results: FVIII in vitro bioequivalence was dependent on trigger type, concentration, and TGA parameter. The mean FVIII in vitro bioequivalence of Mim8 was 36.8% and 16.4% for emi-SIA, based on peak thrombin using a commonly-used trigger (1 pM TF) (Figure 1). Generally, the highest FVIII in vitro bioequivalence was observed at trigger conditions where activated factor IX (FIXa) generation is limited (Table 1). This effect was particularly evident for Mim8.

Conclusion(s): FVIII in vitro bioequivalence for Mim8 was 6.1–36.8% versus 4.7–16.4% for emiSIA, depending on assay conditions. Given the large span in estimated FVIII in vitro bioequivalence for both molecules, its translation to clinical efficacy is currently unknown. Mim8 had a higher thrombin peak in conditions with limited FIXa compared with emi-SIA, suggesting MoA differences.

Novel FVIIIa-mimetic molecule with the potential to be the first oral treatment for severe haemophilia A (ISTH OC 21.1)

Jacob Lund et al

Background: The FVIIIa-mimetic approach has enabled subcutaneous prophylactic treatment of haemophilia A (HA) with weekly to monthly dosing frequency, reducing the treatment burden for patients. An orally available treatment may constitute the next frontier in the management of severe to moderate HA, eliminating injections altogether. However, oral delivery of large molecules constitutes a great technical challenge and requires extensive optimization of potency, biophysical properties and formulation. Novo Nordisk is developing Inno8, a novel VHH-based FVIIIa-mimetic molecule with ultra- high potency to enable once-daily oral treatment of HA.

Aims: To develop the first ever oral FVIIIa mimetic treatment for haemophilia A

Methods: In vitro potency was assessed using thrombin generation assay with HA plasma and thromboelastography with FVIII-neutralized healthy whole blood. Inno8 was formulated with sodium N- [8-(2-hydroxybenzoyl)amino] caprylate (SNAC) for peroral delivery. Oral absorption and systemic plasma half-life were estimated in beagle dogs.

Results: Inno8 was made by connecting two heavy-chain only VHH fragments recognizing human FIXa and FX, respectively, followed by extensive protein engineering to enhance the in vitro potency. With a total molecular weight of approximate 30 kDa, Inno8 is five times smaller than an IgG antibody. Inno8 was further engineered to bind human serum albumin in circulation thereby extending the plasma half-life. Using in vitro global hemostatic assays, Inno8 was demonstrated to achieve similar in vitro activity as the sequence-identical analogue of emicizumab at approximately 90-fold lower concentrations (figure 1). Moreover, Inno8 was shown to be orally available and exhibited a long systemic half-life of approximately 113 hours in beagle dogs. The Inno8 profile may thus allow for prophylactic once-daily oral treatment of HA.

Conclusion(s): Inno8 is a novel, small FVIIIa-mimetic bi-domain antibody with ultra-high potency, long plasma half-life and oral absorption demonstrating potential as the first ever oral treatment of severe HA.

Factor Replacement Therapies

Efanesoctocog Alfa Prophylaxis for Patients with Severe Haemophilia A

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 (OC 50.2, ISTH 2024)

Manuela Albisetti et al

Background: Efanesoctocog alfa (formerly BIVV001) is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to overcome the von Willebrand factor–imposed half-life ceiling. Once- weekly efanesoctocog alfa 50 IU/kg was well tolerated and provided highly effective bleed protection and factor activity within normal to near-normal levels (>40%) for 3 days, and of ~10% at Day 7, in children with severe haemophilia A in the XTEND-Kids study.

Aims: Evaluate long-term data on safety and efficacy of efanesoctocog alfa in previously treated children with severe haemophilia A in the XTEND-ed study (NCT04644575; first interim analysis).

Methods: XTEND-ed is a multicenter, open-label study that enrolled participants from previous Phase 3 studies, including children < 12 years of age who received weekly efanesoctocog alfa prophylaxis for ≤52 weeks in XTEND-Kids, and continue weekly 50 IU/kg prophylaxis in XTEND-ed. The primary endpoint is the occurrence of FVIII inhibitors. Secondary endpoints include annualized bleed rates (ABRs), efficacy for bleed treatment, and safety. Participants provided informed consent and XTEND-ed was approved by applicable ethics committees. Data cut: June 8, 2023.

Results: Seventy-one of 74 males (96%) rolled over from XTEND-Kids to XTEND-ed. The mean (standard deviation [SD]) efficacy period was 35.8 (14.1) weeks. No FVIII inhibitors were detected. The mean (SD) ABR was 0.70 (1.27; 6-monthly data: Table 1), 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. Overall, 43 (61%) participants experienced ≥1 treatment-emergent adverse event (TEAE) and 2 (3%) experienced ≥1 serious TEAE (Table 2).

Conclusion(s): 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.

Quality of life in children with haemophilia A: Phase 3 XTEND-kids study of efanesoctocog alfa (PO134, EAHAD 2024)

M. Carcao et al

Introduction: Haemophilia A is a rare, genetic bleeding disorder characterised by recurrent joint bleeds, leading to reduced mobility and poor quality of life (QoL). This analysis aimed to evaluate QoL in children receiving efanesoctocog alfa (ALTUVIIIO®; formerly BIVV001), a high-sustained factor VIII (FVIII) therapy, in the XTEND-Kids study.

Methods: XTEND-Kids (NCT04759131), a Phase 3, open-label, multicentre study, assessed the safety, efficacy and pharmacokinetics of once-weekly efanesoctocog alfa prophylaxis in previously treated participants aged <12 years with severe haemophilia A. QoL was assessed using patient-reported outcome (PRO) measures completed at baseline, Week 26 and Week 52 (end-of-treatment) by patients or caregiver proxies. PROs included the haemophilia-specific Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL; ≥4 years old, lower scores = better QoL), and the generic Patient-Reported Outcomes Measure Information System (PROMIS) Pain Intensity assessment [0 (no pain) to 10 (worse pain)] and EQ- 5D-Y (scoring: no, some or a lot of problems; dimensions: mobility, looking after myself, usual activities, pain/discomfort, feeling worried/sad/unhappy).

Results: In total, 74 boys were enrolled; mean (SD) age 6.0 (2.9) years. Prior to enrolment, 73 (98.6%) were on FVIII prophylaxis, with one receiving an on-demand regimen. Mean (SD) Haemo-QoL Total scores trended towards improvement from baseline to Week 52 for the following age groups: children 8–<12 years (n = 10), −9.79 (12.18); caregiver proxy 8–<12 years (n = 9), −4.05 (10.77); children 4−7 years (n =14), −2.46 (10.49); caregiver proxy 4−7 years (n = 23), −2.85 (11.82). Most improved Haemo-QoL domains at Week 52 reported by children aged 8–<12 years (n = 10) were 'Other People' (−17.50 [17.87]) and 'Sports and School' (−16.25 [20.67]). Mean (SD) baseline PROMIS Pain Intensity scores (5 to <12 years, assessed by proxy) were low (1.1 [1.95]; n = 29). Overall, children and caregivers reported no problems from baseline to Week 52 across all EQ-5D-Y dimensions.

Discussion/Conclusion: Improvements in QoL were observed in children using a haemophilia-specific PRO measure; however, impact of treatment could not be well captured using generic PRO tools. Baseline PRO scores for pain were low, likely due to lack of chronic joint damage and effects from haemophilia A, given patients' young age and prophylaxis use prior to study, hence improvements were difficult to observe.

First interim analysis of clinical outcomes in adults and adolescents with severe haemophilia A receiving efanesoctocog alfa prophylaxis in XTEND-ed, a phase 3 long-term extension study (OC 50.1, ISTH 2024)

Sophie Susen et al

Background: 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 prophylaxis, was well tolerated, and provided FVIII activity within the normal to near-normal (>40%) range for most of the week.

Aims: Evaluate long-term safety and efficacy of efanesoctocog alfa in adults/adolescents with severe haemophilia A from XTEND-ed (NCT04644575; first interim analysis).

Methods: Previously treated patients (≥12 years old) who completed XTEND-1 (Arm A/B) could continue once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis in the multicenter, open-label, long-term XTEND- ed study. The primary endpoint is incidence of FVIII inhibitor development. Secondary endpoints include annualized bleed rates (ABRs), efficacy for bleed treatment, and safety. XTEND-ed was approved by local ethics committees; participants provided informed consent. Data cut: June 8, 2023.

Results: A total of 146 patients (including 1 female) rolled over from XTEND-1 to XTEND-ed (12–17 years, n=21; 18–64 years, n=120; ≥65 years, n=5). Mean (range) treatment duration in XTEND-ed was 82.5 (14.1– 103.6) weeks. FVIII inhibitors were not detected. Mean (standard deviation) ABR during XTEND-ed for patients from XTEND-1 Arms A and B was 0.72 (1.26) and 0.42 (0.89), respectively (6-monthly data: Table 1), thus maintaining the low mean ABRs observed in the parent study (Arm A: 0.71; Arm B: 0.69). Most (94%; 142/151) bleeding episodes resolved with 1 injection of efanesoctocog alfa; response was rated by participants as excellent/good for 88% (108/123) of bleeds. Overall, 108 (74%) participants experienced
≥1 treatment-emergent adverse event (TEAE) and 17 (12%) experienced ≥1 serious TEAE (Table 2).

Conclusion(s): Long-term results in adults/adolescents in XTEND-ed show that once-weekly efanesoctocog alfa continues to be well tolerated and highly effective. No inhibitors were detected and ABRs remained low.

Interim analysis of joint outcomes in adult and adolescent patients with severe haemophilia A receiving efanesoctocog alfa during the phase 3 XTEND-ed long-term extension study (OC 01.4, ISTH 2024)

Annette von Drygalski et al

Background: Hemophilic arthropathy and chronic joint pain from repeated bleeding episodes in haemophilia A may

occur despite standard-of-care prophylaxis. In XTEND-1 (NCT04161495), once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis was well tolerated, providing highly effective bleed protection and high-sustained factor VIII activity levels across the weekly dosing interval.

Aims: Assess long-term joint health with efanesoctocog alfa prophylaxis in adults/adolescents from XTEND-1 who continued to the extension study, XTEND-ed (NCT04644575).

Methods: XTEND-ed is an open-label, multicenter study of previously treated patients with severe haemophilia A. Participants provided informed consent; the study was approved by applicable review boards. Changes from parent study (XTEND-1) baseline to Month 12 in XTEND-ed in Haemophilia Joint Health Scores (HJHS) and target joint resolution for participants aged ≥12 years who received once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis are presented descriptively (data cutoff June 8, 2023). Individual joints (left/right elbows, knees, and ankles) were scored according to 8 HJHS domains; gait was also assessed. Total HJHS score encompasses joint and gait score. Target joints were evaluated based on International Society on Thrombosis and Haemostasis criteria.

Results: Arm A of XTEND-ed enrolled 146 participants from XTEND-1 (additional mean [standard deviation, SD] treatment duration 82.5 [14.3] weeks). By Month 12 in XTEND-ed, joint health had improved or been maintained in evaluable participants compared with XTEND-1 baseline, as measured by HJHS total score, total joint score, and subdomain scores (Figure, Table). The HJHS domain with the greatest mean (SD) change from baseline to Month 12 was flexion loss -0.6 (2.7). At XTEND-1 baseline, there were 140 target joints among 45 participants; at 1 year, all target joints (n=132) had resolved in participants exposed for ≥12 months (n=43).

Conclusion(s): Interim results from XTEND-ed indicate that once-weekly prophylaxis with efanesoctocog alfa is associated with improvement or maintenance of joint health in adults and adolescents.

Perioperative management with efanesoctocog alfa in adults, adolescents, and children with severe haemophilia A in the phase 3 XTEND clinical program (OC 14.1, ISTH 2024)

Anthony Chan et al

Background: Efanesoctocog alfa (formerly BIVV001) is a first-in-class high-sustained factor VIII replacement therapy that provides effective bleed prevention with once-weekly dosing (50 IU/kg) in previously treated patients with severe haemophilia A.

Aims: Evaluate efficacy and safety of efanesoctocog alfa for perioperative management in the Phase 3 XTEND clinical program.

Methods: XTEND-1 (NCT04161495) and XTEND-Kids (NCT04759131) studies assessed safety and efficacy of efanesoctocog alfa in previously treated patients ≥12 and < 12 years old, respectively, with severe haemophilia A. Participants from each study could continue treatment in the XTEND-ed study (NCT04644575). Participants provided informed consent, and studies were approved by ethics committees. Participants undergoing surgery were to receive a pre-operative loading dose of efanesoctocog alfa 50 IU/kg. For major surgeries, post-operative doses of 30 or 50 IU/kg every 2–3 days were allowed. Surgery endpoints included dose, number of injections, hemostatic response, factor consumption, blood loss, and blood transfusions during the perioperative period. Interim data cut: January 17, 2023.

Results: Forty-one participants (< 18 years, n=9; ≥18 years, n=32) underwent 49 major surgeries (Table 1); 23 were orthopedic surgeries, with knee arthroplasty most common (n=12). All single 50 IU/kg pre- operative doses maintained hemostasis during major surgery. Median (range) number of doses per major surgery was 4.0 (1–7) during the perioperative period (Days −1 to 14). Hemostatic response was rated excellent for 43 surgeries and good for 5 surgeries. Median (range) blood loss was 20 (0–1000) mL during surgery (n=29); red blood cell transfusion was required for 1 total knee replacement. Of 32 minor surgeries (Table 2) among 28 participants, 27 were managed with 1 pre-operative dose

and 5 with no pre-operative dose. Of those with an assessment (n=25), all hemostatic responses were rated excellent.

Conclusion(s): Efanesoctocog alfa was effective and well tolerated for perioperative management in participants with severe haemophilia A.

Gene Therapy

Valoctocogene roxaparvovec (Roctavian)

Safety and efficacy of valoctocogene roxaparvovec in participants with active and prior FVIII inhibitors: Preliminary results from GENEr8-INH, a phase 1/2 study (OR10, EAHAD 2024)

Guy Young et al

Introduction: Valoctocogene roxaparvovec is a gene therapy licensed in the EU and US for individuals with severe haemophilia A (sHA) without adeno-associated virus serotype 5 (AAV5) antibodies and factor VIII (FVIII) inhibitors. We present interim results for the first individuals treated with active or prior inhibitors.

Methods: GENEr8-INH (NCT04684940) is a phase 1/2 trial evaluating safety and efficacy of valoctocogene roxaparvovec (6 × 1013 vg/kg) in anti-AAV5–negative sHA participants and active (part A) or prior (part B) FVIII inhibitors. Prophylactic corticosteroid (CS) started on day 15 (part A) and day 1 (part B). Primary outcome was treatment-related adverse events (AEs). Secondary outcomes included change from baseline in FVIII activity, change in FVIII inhibitor titter (part A) or recurrence (part B), change in annualized prophylactic or on-demand HA therapy, and annualized treated bleeds. As emicizumab use was permitted, a chromogenic assay with bovine reagents was used for FVIII and FVIII inhibitor assessment. Two participants enrolled in part A and B; expansion is dependent on data monitoring committee evaluation (week 12).

Results: Participants 1 and 2 in part A (PAP1 and PAP2) received emicizumab for >2 years prior to enrolment. Their inhibitor titter, 3.8 and 2.2 BU/mL at screening, peaked by 12 weeks post-infusion. Inhibitors declined in PAP1 but rose after an AE of elevated alanine aminotransferase (ALT) that was treated with increased CS. For PAP2, inhibitors declined from 20.1 BU/mL (week 9) to <0.6 BU/mL (week 32). At this time, FVIII activity peaked (41.7 IU/dL) and FVIII B-domain–deleted antigen was 26.0 ng/mL. In part B, participants 1 and 2 (PBP1 and PBP2) had prior immune tolerance induction therapy and inhibitor titters <0.6 BU/mL at screening. FVIII activity for PBP1 and PBP2 reached 26.2 and 247.8 IU/dL, respectively. In the available 32-week follow-up, inhibitor titters did not recur. The most common AEs were non-serious ALT elevations (PAP1, PBP1 and PBP2) and grade 1 non-serious AEs related to CS use (moon face, acne, and weight gain). No serious or severe AEs were reported, including malignancy, FVIII inhibitor recurrence in part B, or thromboembolism.

Discussion/Conclusion: To date, valoctocogene roxaparvovec has a similar safety profile in participants regardless of inhibitor status. Interim efficacy results are encouraging.

Seven-year follow-up of valoctocogene roxaparvovec gene therapy for haemophilia A (OC 30.1, ISTH 2024)

Bella Madan et al

Background: Valoctocogene roxaparvovec is an adeno-associated virus vector serotype 5 (AAV5)- mediated gene therapy approved for severe haemophilia A (HA).

Aims: The aim is to update on seven-year follow-up of valoctocogene roxaparvovec gene therapy for haemophilia A.

Methods: In this open-label, phase 1/2 dose-escalation trial (NCT02576795), males ≥18 years with severe HA (factor

VIII [FVIII] ≤1 IU/dL) who were previously receiving exogenous FVIII and had no history of FVIII inhibitors or anti-AAV5 antibodies received an infusion of 6x1013 (n=7) or 4x1013 (n=6) vg/kg valoctocogene roxaparvovec. Efficacy was assessed by FVIII activity (chromogenic assay), bleeding and exogenous FVIII use; safety was assessed with reported adverse events.

Results: At years 7 and 6, median (interquartile range) FVIII activity was 10.3 (4.8–14.2) and 7.2 (4.5–8.9) IU/dL in the 6x1013 (n=5) and 4x1013 (n=4) cohorts, respectively. In the last year, estimated FVIII activity changed by −0.001 and −0.07 IU/dL/week for the 6x1013 and 4x1013 cohorts, respectively. During all follow-up, mean ABRs decreased from BL by 96% and 88% for the 6x1013 and 4x1013 cohorts at years 7 and 6, respectively. A 6x1013 cohort participant resumed prophylaxis after a non–treatment-related grade 4 SAE of spontaneous internal carotid artery bleeding in year 7. Another 6x1013 cohort participant resumed prophylaxis in year 7 following ankle joint bleeds; 6 weeks prior, his FVIII activity was 1.9 IU/dL. A 4x1013 cohort participant transiently returned to prophylaxis during year 5. Mean (median) annualized FVIII infusion rate for the 6x1013 and 4x1013 cohorts were 6.4 (1.6) and 9.3 (5.1) infusions/year over all follow-up, a decline of 95% and 93% from BL, respectively. In the last year, 1 participant in each cohort had a treatment-related AE: grade 1 hepatomegaly (6x1013) and grade 1 splenomegaly (4x1013).

Conclusion(s): While 2 participants resumed prophylaxis in year 7, the majority maintained haemostasis. Safety remains in line with previous reports.

Efficacy and safety of valoctocogene roxaparvovec 4 years after gene transfer in GENEr8-1 (OC 30.2, ISTH 2024)

Andrew D. Leavitt et al

Background: Valoctocogene roxaparvovec (AAV5-hFVIII-SQ), a gene transfer therapy for severe haemophilia A, enables endogenous factor VIII (FVIII) production to prevent bleeding.

Aims: Evaluate efficacy and safety outcomes 4 years post-valoctocogene roxaparvovec treatment.

Methods: In the open-label, multicenter, phase 3 GENEr8-1 trial (NCT03370913), 134 adult men with severe haemophilia A (FVIII ≤1 IU/dL) without FVIII inhibitors received 6E13 vg/kg valoctocogene roxaparvovec (intention-to-treat [ITT] population). Bleeds and FVIII use were self-reported after regular prophylaxis cessation (scheduled week [W]4). The rollover population, which included 112 HIV-negative participants who enrolled from a non-interventional study, was used for comparisons with baseline FVIII use and bleeding rate. Chromogenic (CSA) and one-stage assay (OSA) FVIII activity was assessed in 132 HIV-negative participants (modified ITT [mITT] population). Safety was assessed in the ITT population.

Results: In the ITT population, 118/134 participants completed W208; 24/134 participants resumed prophylaxis. In the rollover population, mean annualized treated bleeding rate was 0.8 bleeds/y, mean annualized bleeding rate for all bleeds was 1.3 bleeds/y, and mean annualized FVIII infusion rate was 6.1 infusions/y over 4 years (Table). 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 W208, mean CSA and OSA FVIII activity was 16.1 and 27.1 IU/dL, respectively, in the mITT population (18.0 and 25.5 IU/dL at W260 for the mITT subgroup dosed ≥5 years prior; Figure); 10/130 (7.7%), 68/130 (52.3%), 18/130 (13.8%), and 34/130 (26.2%) participants had CSA FVIII activity ≥40, ≥5 to < 40, ≥3 to < 5, and < 3 IU/dL, respectively. 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.

Conclusion(s): Bleed control and FVIII expression were maintained 4 years post-valoctocogene roxaparvovec treatment. No new safety signals emerged.

Health-related quality-of-life outcomes 4 years after treatment with valoctocogene roxaparvovec (OC 30.3, ISTH 2024)

Bella Madan et al

Background: Valoctocogene roxaparvovec, a gene therapy for severe haemophilia A (HA), helps prevent bleeding by providing the body with genetic instructions for making factor VIII (FVIII) protein. We report findings from the GENEr8-1 study 4 years after participants received valoctocogene roxaparvovec.

Aims: To compare health-related quality-of-life (HRQOL) outcomes before and after treatment with valoctocogene roxaparvovec.

Methods: In GENEr8-1, 134 adult men with severe HA received one infusion of valoctocogene roxaparvovec (6E13 copies of FVIII instructions/kg). To assess their HRQOL, participants completed questionnaires before receiving valoctocogene roxaparvovec and regularly afterwards. The Haemo-QOL- A, a questionnaire designed for HA and B, is being validated for gene therapy for HA. It produces a Total Score reflecting overall HRQOL and domain scores measuring impacts on specific aspects of life, such as Physical Functioning (eg, ability to carry out everyday tasks), Role Functioning (eg, relationships and ability to function in social roles), and Consequences of Bleeding (fear of having a bleed/what happens after you have a bleed). Here, Haemo-QOL-A results are presented for the 132 HIV-negative participants in total and by the participants' FVIII activity level at year 4. Other questionnaires will be included in the final presentation.

Results: Four years after treatment with valoctocogene roxaparvovec, the average Haemo-QOL-A Total Score increased by 6.2 points, an average improvement considered meaningful to people with severe HA (Table 1). Improvements were also seen for Physical Functioning (4.8 points), Role Functioning (5.9 points), and Consequences of Bleeding (9.2 points). At year 4, average Haemo-QOL-A Total Score increased by 6.3, 5.8, and 6.9 points for year 4 FVIII activity in ranges ≥40%, ≥5% to < 40%, and < 5%, respectively (Table 2).

Conclusion(s): Valoctocogene roxaparvovec provides HRQOL improvements considered meaningful for people with severe HA over 4 years, even for participants with FVIII levels below 5% at year 4.

Dirloctocogene Samoparvovec (SPK-8011)

Long-Term Follow-Up of Participants in the Phase I/II Trial of Dirloctocogene Samoparvovec (SPK-8011): Durable FVIII Expression and Clinically Meaningful Reduction of Bleeding (OC 02.4, ISTH 2024)

Stacy E. Croteau et al

Background: Dirloctocogene samoparvovec (SPK-8011) is an investigational adeno-associated viral vector gene therapy for haemophilia A (HA). Previous Phase I/II trial (NCT03003533/NCT03432520) interim analysis indicated dirloctocogene samoparvovec was well tolerated; participants had sustained factor (F)VIII activity (cut-off: June 30, 2022; Croteau, ASH 2022).

Aims: Describe long-term safety and efficacy of dirloctocogene samoparvovec and novel non-steroid immune prophylaxis (tocilizumab, mycophenolate mofetil) use in the Phase I/II trial.

Methods: In this single-arm trial, adult males with moderate–severe HA received dirloctocogene samoparvovec (George, NEJM 2021).

Results: At cut-off (October 10, 2023), 25 participants were enrolled across dosing cohorts of 5×10^11 vg/kg (n=2), 1×10^12 vg/kg (n=3), 1.5×10^12 vg/kg (n=11), or 2×10^12 vg/kg (n=9). Median time since dosing was 220.6 weeks

(range: 45.3–340.3). Sixty-six treatment-related adverse events occurred: 37 immunomodulation-related, 29 vector-related, including one serious Grade 2 alanine transaminase (ALT) elevation with elective hospitalization for intravenous corticosteroids. No FVIII inhibitors or thrombotic events occurred. In Year 1, 16 participants had transient ALT rise ≥1.5 fold over baseline; median time until rise was 40.5 days (Q1–Q3: 20.5–71.5). FVIII expression was sustained in most participants (Figures). Three participants returned to prophylaxis. Median annualized bleed rate (ABR) post dirloctocogene samoparvovec administration was 0.2 (Q1–Q3: 0.0–3.2) vs historical ABR 5.0 (1.0–11.0) on prior prophylaxis (n=20), and 0.3 (0.2–0.5) vs historical ABR 30.0 (15.0–36.0) for on-demand treatment (n=5). Median annualized FVIII infusion rate (AIR) was 1.5 (Q1–Q3: 0.0–5.6) post vector administration vs historical AIR on prophylaxis 104.0 (57.5–156.0) and 0.6 (0.3–1.0) vs historical AIR 33.0 (30.0–36.0) for on- demand treatment.

Conclusion(s): Up to 7 years post dirloctocogene samoparvovec administration, data indicate that investigational gene therapy was well tolerated, with durable FVIII expression and clinically meaningful ABR and AIR reductions. Non-steroid immune prophylaxis did not abrogate use of steroids to treat presumed immune response.

AAV-HLP-hFVIII-V3

Stable expression of factor VIII over 5 years following adeno-associated viral vector-mediated gene transfer in participants with severe haemophilia A using a novel human factor VIII variant (OR05, EAHAD 2024)

P. Chowdary et al

Introduction: GO-8 (ClinicalTrials.gov: NCT03001830) is a study of liver-directed adeno-associated virus (AAV) gene therapy for severe haemophilia A (SHA) using a factor VIII (FVIII) variant containing a 17 amino- acid peptide comprising six N-linked glycosylation motifs from the human FVIII B-domain (AAV-HLP-hFVIII- V3).

Methods: In a multi-centre, open-label, phase I/II clinical trial, we assessed the safety and efficacy of escalating doses of AAV-HLP-hFVIII-V3 pseudotyped with an AAV8 capsid in adults with SHA (FVIII activity ≤1%). Participants received prophylactic immunosuppression to reduce the risk of vector-related transaminase elevation. The primary endpoints were safety, and efficacy assessed by FVIII activity (FVIII: C).

Results: As of May 31 2023, 12 participants were enrolled into one of four vector doses: 6 × 1011 vector genomes (vg)/kg t (n = 1), 2 × 1012 vg/kg (n = 3), 4 × 1012 vg/kg (n = 3), or 6 × 1012 vg/kg (n = 5). The most common vector-related adverse event was elevation in liver aminotransferase levels, which occurred in 10 of 12 participants within 12 months. Mean chromogenic FVIII: C levels at 12 months after gene therapy were 3 IU/dL in the 6 × 1011vg/kg cohort, 13 ± 9 IU/dL (range: 2−19 IU/dL) in the 2 × 1012vg/kg cohort, 8± 1 IU/dL in the 4 × 1012 vg/kg cohort (range: 7−9 IU/dL) and 22 ± 34 IU/dL in the 6 × 1012 vg/kg cohort (range 1−82 IU/dL). Transgene expression was stably maintained over a median follow-up of 3 years (range: 2–5 years) from the level achieved 1-year post-infusion, best illustrated by the data from the 2 × 1012 and 4 × 1012 vg/kg cohorts. Nine of the 12 participants remained off prophylaxis post-gene therapy. Median (mean) annualised FVIII consumption reduced from 4097 IU/kg (4657) per year at baseline to 61 IU/kg (1186), that was significant (One sample t-test p = 0.0009). No FVIII inhibitors or thrombotic events were reported for the duration of the study.

Discussion/Conclusion: A single infusion of AAV-HLP-hFVIII-V3 resulted in stable FVIII expression over a follow-up period of up to 5 years in participants with SHA. A high rate of liver aminotransferase elevation following gene transfer impacted transgene expression. However, nine of the 12 participants were able to discontinue FVIII prophylaxis over the duration of the study, resulting in a significant reduction in FVIII concentrate usage.

Gene Therapy

Etranacogene dezaparvovec (Hemgenix)

Response to gene therapy in haemophilia B: Ranges of factor IX sustained after 3 years in HOPE-B etranacogene dezaparvovec gene therapy trial (FP-006, WFH 2024)

Cedric Hermans et al

Introduction and Objective: The Phase 3 HOPE-B trial (NCT03569891) assesses etranacogene dezaparvovec, a gene therapy for haemophilia B comprising an adeno-associated virus 5 (AAV5) vector and codon-optimised factor IX (FIX) Padua R338L transgene under the control of a liver-specific promoter. Aim of this report is to communicate FIX levels at 3 years post-treatment.

Material and Methods: Adult male participants (n = 54) with severe or moderately severe haemophilia B (FIX ≤2%) were treated in the Phase 3, open-label, single-arm, pivotal HOPE-B trial with a one- timeintravenous infusion of 2 X 1013 gc/kg etranacogene dezaparvovec, following a ≥6-month lead-in period of FIX prophylaxis.
Results: Of 54 participants dosed, 2 (3.7%) participants - one with the highest AAV5 NAb titre 1:3212 and one who received partial dose - did not express FIX Padua and remained on FIX prophylaxis. FIX levels were missing/ uninterpretable for 4 (7.4%) patients: (one died [unrelated to treatment], one returned to FIX continuous prophylaxis at month 30 post-treatment following decline of FIX expression to levels 2%– 5% and bleeding phenotype recurrence, one had a liver transplant, one participant's sample was unsuitable for analysis. By year 3, 1 (1.9%) patient expressed endogenous FIX activity levels <5 IU/dL, 3 (5.6%) between 5–< 12 IU/dL), 12–< 40 IU/dL for 26 (48.1%), and >40 IU/dL for 18 (33.3%). At 3 years post- treatment, the mean +- SD(median; range) FIX activity level of participants was 38.6 IU/dL +- 17.8 (36.0; 4.8–80.3) for the 48 patients for whom endogenous FIX levels were available and interpretable. Median [IQR;max] bleeds per participant decreased from 2.0 [0–4;10] during the lead-in period and remained stable to 0.0 [0–0;4] during Year 1, 0.0 [0–1:10] during Year 2 and 0.0 [0–0;8] during Year 3. During the 3 years post-dose, therewere no serious AEs related to treatment. There were no serious adverse events (AE) related to treatment. No late treatment-related ALT elevations or thromboembolic events were reported. Overall safety profile remained favourable and consistent with previous observations.

Conclusions: One-time infusion of etranacogene dezaparvovec resulted in stable FIX expression, with 53.7% patients maintaining mild- and 33.3% maintaining non-haemophilia (>40 IU/dL) FIX activity levels at 3 years post-treatment.

First report of a long-term follow-up extension study 6 years after gene therapy with AMT-060 in adults with haemophilia B confirms safety and stable FIX expression and sustained reductions in factor IX use (OR03, EAHAD 2024)

W. Miesbach et al

Introduction: AMT-060 is an adeno-associated virus serotype 5 (AAV5) vector encoding a codon- optimised wild-type human factor IX (FIX) gene, driven by a liver-specific promoter. As the predecessor of etranacogene dezaparvovec (Padua FIX variant), it has a same vector backbone, except the two-nucleotide change in the human FIX coding sequence which enhances FIX activity. The Phase I/II study included 10 patients with haemophilia B (FIX activity ≤2 IU/dL) who received a single intravenous infusion of AMT-060 (5 × 1012 gc/kg [Cohort 1; n = 5] or 2 × 1013 gc/kg [Cohort 2; n = 5]). Nine out of ten patients were prophylaxis free after administration of AMT-060. Using the one-stage activated partial thromboplastin time (aPTT) assay, mean FIX activity as reported initially was 4.4 IU/dL at 52 weeks in Cohort 1 and

6.9 IU/dL at 26 weeks in Cohort 2.

Methods: Patients who successfully completed all assessments during 5 years of follow-up in the study were enrolled in the open-label, Phase I/IIb extension study (NCT05360706). Here, we report the first year of follow-up in the extension study; representing 6 years after AMT-060 administration.

Results: Overall, four patients from Cohort 1 (including one patient who remained on FIX prophylaxis) and five patients from Cohort 2 enrolled in the extension study. FIX activity, using the one-stage aPTT assay, remained stable at Year 6; ranging from 3.1−14.8 IU/dL in Cohort 1 and 3.0−7.1 IU/dL in Cohort 2. Mean (SD) and median FIX activity were 7.5 IU/dL (6.4) and 4.6 IU/dL in Cohort 1, and 5.5 IU/dL (1.5) and 5.8 IU/dL in Cohort 2, respectively. Mean (SD) annualised FIX consumption during Year 6 (excluding surgeries and patient who remained on FIX prophylaxis) was 656.3 (1136.8) IU/year (or 7.5 [12.9] IU/kg/year) in Cohort 1 (n = 3) and 0 in Cohort 2 (n = 5). No new safety events were identified during Year 6, and no patient returned to prophylaxis.

Discussion/Conclusion: Gene therapies for haemophilia A and B, including etranacogene dezaparvovec, were recently authorised in Europe. Durability of factor expression is a key consideration in the decision- making process for patients and physicians. This 6-year follow-up after AMT-060 administration confirms the safety, durability and stability of FIX expression after AAV-based gene therapy reported previously.

Etranacogene dezaparvovec haemophilia B gene therapy phase 2b trial final results: stable and durable FIX level expression over 5 years (OC 02.3, ISTH 2024)

Sandra le Quellec et al

Background: Etranacogene dezaparvovec is the first approved gene therapy for haemophilia B (HB). It is a recombinant adeno-associated virus serotype 5 (AAV5) vector comprising a codon-optimized FIX Padua variant transgene under the control of a liver-specific promoter, differing by 2 nucleotides from its predecessor (AMT-060).

Aims: To investigate FIX levels following etranacogene dezaparvovec treatment in adults with HB (FIX levels ≤2%).

Methods: Phase 2b, open-label, multi-center trial (NCT03489291) in which 3 HB patients on routine prophylaxis received a single intravenous dose of etranacogene dezaparvovec (2×1013 gc/kg) and were followed for 5 years. Informed consent was obtained and the study was approved by the institutional review board/ethic committee at each center. Secondary endpoints included laboratory parameters, bleeding rates and adverse events.

Results: All 3 participants had neutralizing antibodies (NAbs) to AAV5 at mean titer of 25 at dosing. Mean aPTT-based FIX activity remained stable throughout the trial duration: from Year 1 (40.7%) to Year 5 (46.7%). At Year 5 post-dose, FIX activity measured 46.8%, 39.0% and 51.2% in the 3 participants, respectively. Mean and median ABR for the cumulative follow-up period Years 0–5 was 0.14 and 0, respectively, for all bleeds. One participant experienced 2 bleeds (1 traumatic and 1 spontaneous muscle bleed, both treated with on-demand FIX) during Year 1 post-dose and none thereafter, and 2 participants were free from any bleeds over 5 years. Consequently, no patients returned to FIX prophylaxis. Safety profile was favorable throughout study follow-up: there were no treatment-related serious adverse events, clinically significant liver enzyme elevations, FIX inhibitor development or thromboembolic events.

Conclusion(s): Sustained and stable FIX activity post-etranacogene dezaparvovec administration was observed over 5 years, enabling discontinuation of routine prophylaxis, irrespective of anti-AAV5 NAbs at baseline. Patients have been offered to enroll in the extension study (NCT05962398) for an additional 10- year follow-up.

IX-TEND: A Phase IV Observational, Long-term Follow-up Study on the Safety and Efficacy of Etranacogene Dezaparvovec in Patients with Haemophilia B (PB0541, ISTH 2024)

Andreas Tiede et al

Background: Haemophilia B therapy goals include prevention and treatment of spontaneous bleeding episodes, but the current standard-of-care, factor IX (FIX), is not curative. Etranacogene dezaparvovec is an adeno-associated virus type 5 vector containing a highly active FIX Padua transgene approved in the US and Europe. The Phase 3 HOPE-B trial (NCT03569891) in patients with haemophilia B given etranacogene dezaparvovec demonstrated significant reduction in bleeding and FIX consumption with a favorable safety profile; long-term data are needed to assess its durability and safety in a larger population.

Aims: To evaluate the short- and long-term safety and effectiveness of etranacogene dezaparvovec in a larger population of adults with haemophilia B.

Methods: This Phase 4, observational, post-authorization, long-term follow-up, multicenter, international study (NCT06008938) investigates etranacogene dezaparvovec in adults with haemophilia B who have provided informed consent. Two cohorts (each targeting enrollment of n~250) will include patients with haemophilia B given either 1) commercially available etranacogene dezaparvovec as a single intravenous infusion, or 2) FIX prophylaxis while enrolled in the US American Thrombosis and Hemostasis Network Transcends: Natural History Observational Cohort Study or in local registries in other countries (Figure). For both cohorts, patients will be enrolled 5 years from enrollment of the first patient treated post- approval (June 15, 2023) and followed for 15 years. Effectiveness and safety data during and after treatment at predetermined timepoints, as well as medical history, will be collected. Formal hypothesis testing is not planned, hence control for type I error is not required.

Results: Primary and secondary endpoints are summarized (Table). First analysis of results is planned after ~50 patients have completed 1 year follow-up. Final report is expected in 2044.

Conclusion(s): This study will provide long-term data on the effectiveness and safety of etranacogene dezaparvovec and build on its efficacy and safety profile in a larger population.

Etranacogene dezaparvovec shows sustained efficacy and safety in adult patients with severe or moderately severe haemophilia B 3 years after administration in the Hope-B Trial (OR09, EAHAD 2024)

S. Pipe et al

Introduction: Etranacogene dezaparvovec (formerly AMT-061) is the first approved gene therapy for haemophilia B in the EU and US. The HOPE-B pivotal phase 3 clinical trial (NCT03569891) demonstrated superior bleed protection compared to FIX prophylaxis up to 24 months post-treatment with ongoing follow-up from Year 2 onward. Here, we report efficacy and safety during Years 1–3.

Methods: In this pivotal phase 3 open-label, single-arm trial, adult male patients (pts) with severe or moderately severe haemophilia B, with or without preexisting adeno-associated virus serotype 5 (AAV5) neutralising antibodies, received a single dose of etranacogene dezaparvovec (2 X 1013 gc/kg, an AAV5 vector containing factor IX [FIX] Padua R338L transgene under the control of the liverspecific LP-1 promoter) following ≥6-month lead-in period of FIX prophylaxis.

Results: Of 54 pts receiving etranacogene dezaparvovec, 52 completed 36 months follow-up. Mean annualised bleeding rate (ABR) for all bleeds during Months 7–36 was reduced by 64% versus lead-in (1.52 and 4.17, respectively; P = 0.0004). Mean SD endogenous FIX activity was sustained at 41.5 IU/dL +-21.7 (n = 50), 36.7 IU/dL+- 19.0 (n = 50), and 38.6 IU/dL 17.8 (n = 48) at Years 1, 2 and 3 post-treatment, respectively. At 3 years post-treatment, 51 pts (94%) remained free of continuous FIX prophylaxis; mean annualised FIX consumption decreased by 96% versus lead-in (P < 0.0001). One pt's

FIX levels eventually declined to 2%–5%; his bleeding phenotype returned, and he resumed prophylaxis per protocol at Month 30 post-treatment. All pts experienced at least one adverse event (treatment-emergent AE), with no serious AEs related to treatment (one case of hepatocellular carcinoma [HCC] and one death were reported before Year 2 and unrelated to treatment). A total of 38/54 (70%) pts experienced 96 treatment- related AEs. The most common AE was increased alanine transaminase (ALT). Nine pts (16.7%) received reactive corticosteroids for mean SD 81.4+- 28.6 days. No new deaths, HCC, or late treatment-related ALT elevations were reported during Year 3.

Discussion/Conclusion: A single dose of etranacogene dezaparvovec provides long-term FIX Padua expression and superior bleed protection compared to prophylaxis, with a favourable safety profile over 3 years post-administration.

Adults with haemophilia B and history of chronic HCV/HBV infection receiving etranacogene dezaparvovec gene therapy in the HOPE-B clinical trial demonstrate long-term bleeding protection and sustained fix activity 3 years after administration (PO028, EAHAD 2024)

A. von Drygalski et al

Introduction: Etranacogene dezaparvovec (formerly AMT-061) has recently become a therapeutic option for patients (pts) with haemophilia B (HB) and comorbid chronic hepatitis C virus (HCV) and hepatitis B virus (HBV). The pivotal phase 3 HOPE-B trial (NCT03489291) evaluated etranacogene dezaparvovec in pts with severe or moderately severe HB; here we evaluate the efficacy and safety in the subset of pts with a history of chronic HCV and/or HBV over 3 years post-treatment.

Methods: Adult males with haemophilia B (factor IX [FIX] ≤2%), were infused with a single dose of etranacogene dezaparvovec (2 × 1013 gc/kg; an adeno-associated virus serotype 5 (AAV5) vector containing FIX Padua R338L transgene under the control of the liver-specific promoter LP-1), following a ≥6-month lead-in period of FIX prophylaxis. Exclusion criteria included baseline liver chemistries > 2× upper limit of normal; active HCV/HBV or uncontrolled HIV infection; or advanced liver fibrosis (FibroScan score ≥9 kPa).

Results: Of 54 pts in the HOPE-B trial, 31 (57.4%) had comorbid chronic HCV without active disease. Of these, seven had a history of chronic HBV infection without active disease. Two were HCV/HIV co-infected. Two pts were HBV+/HCV–/HIV–. The mean age in HCV/HBV pts (n = 33) was 50.0 years (range, 31–75). Mean ± SD FIX activity was 46.5 ± 23.0, 40.2 ± 20.8 and 44.5 ± 19.0 at Years 1, 2 and 3 in HCV/HBV pts and 34.0 ± 17.8, 31.3 ± 14.6 and 31.0 ± 13.1 at Years 1, 2 and 3 in HCV–/HBV– pts (n = 21). Mean FibroScan score for HCV/HBV pts was 5.2 kPa (range 2.8–8.0). Excluding 1 pt with AAV5 neutralising antibody (NAb) titre of 1:3212, HCV/HBV pts (n = 32) demonstrated ABR ratio of 0.31 (95% CI, 0.13, 0.72), indicating 69% reduction in all bleeding, sustained from months 7–36 posttreatment.

In the HCV/HBV subgroup, 5/33 (15.2%) had ALT elevations, of which 4/33 (12.1%) were treated with corticosteroids versus 11/54 (20.4%) and 9/54 (16.7%) in the whole HOPE-B population, respectively. As reported previously HCV/HBV pt developed a hepatocellular carcinoma (HCC) deemed unrelated to treatment.

Discussion/Conclusion: Patients in the HOPE-B trial with HCV and/or HBV infection show comparable efficacy and safety to the rest of the study population.

Fidanacogene elaparvovec (brand names Durveqtix, Beqvez)

Efficacy and safety of fidanacogene elaparvovec in adults with moderately severe or severe haemophilia B: updated results from the phase 3 BENEGENE-2 gene therapy trial (OC 30.5, ISTH 2024)

Kaan Kavakli et al

Background: Fidanacogene elaparvovec, an adeno-associated virus-based gene therapy, transfers the high-activity

variant of human factor IX (FIX) FIX-R338L for the treatment of haemophilia B.

Aims: To evaluate the efficacy and safety of fidanacogene elaparvovec in participants with moderately severe or severe haemophilia B.

Methods: BENEGENE-2 (NCT03861273) is a phase 3 trial that enrolled adult males with haemophilia B (FIX:C ≤2%) who completed ≥6 months of FIX prophylaxis prior to administration of 5e11 vg/kg fidanacogene elaparvovec. The primary endpoint was non-inferiority on annualized bleeding rate (ABR) for total (treated and untreated) bleeds from Week 12 to Month 15 post-infusion vs the pre-infusion prophylaxis period. Key secondary endpoints included FIX activity, ABR for treated bleeds, and annualized infusion rate. Participants provided written informed consent and the study was approved by the relevant regulatory/ethics committees. This study was sponsored by Pfizer.

Results: Forty-five participants (median [range] age, 29 [18–62] years) were dosed with fidanacogene elaparvovec 5e11 vg/kg. As of August 2023, 44 participants completed ≥15 months follow-up (up to 4.0 years); the 45th participant had >12 months follow-up; we previously reported on 41 with ≥15 months of follow-up). Total ABR was reduced by 71% from Week 12 to Month 15 post-gene therapy vs prophylaxis (mean ABR, 1.3 vs 4.4; P< 0.0001; Table 1). Mean FIX activity measured by one-stage SynthASil, one-stage Actin-FSL, and chromogenic assays is shown in Table 2. FIX activity remained stable at Month 24 in 39 participants (as measured by SynthASil assay) (Table 2). Secondary efficacy endpoints are reported in Table 1. Twenty-eight (62%) participants received corticosteroids for presumed immune response. No deaths, infusion-related serious adverse events, thrombotic events, or FIX inhibitors were reported.

Conclusion(s): Fidanacogene elaparvovec yielded endogenous FIX expression in participants with moderately severe to severe haemophilia B, resulting in significant decreases in bleeding, and was generally well tolerated.

Health-related quality of life in adults with haemophilia B after gene therapy with fidanacogene elaparvovec in the BENEGENE-2 trial (PO116, EAHAD 2024)

S. von Mackensen et al

Introduction: The burden of the management and clinical sequelae of haemophilia B (HB) negatively impacts health-related quality of life (HRQoL), including physical and mental health and functional status. BENEGENE-2 (NCT03861273) is an ongoing phase 3 trial of fidanacogene elaparvovec, an adeno- associated virus gene therapy vector delivering a high-activity factor IX variant, FIX-R338L/FIX-Padua. Patient-reported outcome assessments (PROs) are presented for HRQoL, health status and functional status.

Methods: Adult males with HB (FIX: C ≤2 IU/dL) who completed ≥6 months of FIX prophylaxis received a single infusion of fidanacogene elaparvovec 5e11 vg/kg. Participants completed PROs pre- and post- infusion (Week 52), including the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), Haemophilia Activities List (HAL), EQ-5D-5L, Patient Global Impression of Change–Haemophilia (PGIC-H) and Haemophilia Life Impacts Questionnaire (HLIQ).

Results: At baseline (pre-infusion), the median age was 29 (range 18–62) years (N = 45). Data from pre- infusion to Week 52 were available for up to 42 participants, depending on the assessment/domain. The mean Haem-A-QoL total score decreased from pre-infusion by 11.2 (SD 9.1; p < .001), more than the clinically meaningful 7-point score reduction, suggesting an improvement in HRQoL. Scores for individual domains (including physical health, feeling, view of self, work/school, sport/leisure, treatment, future) also improved over time. For the HAL assessment, mean (SD) Complex Lower Extremity Activities and Basic Lower Extremity Activities component scores improved by 7.6 (19.6; p = .024) and 11.1 (18.2; p <.001), respectively, indicating improved functional status. Improvements in EQ-5D-5L index scores and EQ-VAS (treatment difference [95% CI]: 0.05 (0.02–0.08]; p=.003 and 5.8 (0.6–11.0]; p =.030, respectively) were observed from pre- to post-infusion, indicating improved health status. Most participants (78%) reported at least moderate improvements in their overall impression of life with haemophilia using the PGIC-H and improvements in

most HLIQ domains related to life impacts associated with living with and treating haemophilia.

Discussion/Conclusion: Fidanacogene elaparvovec improved HRQoL, health and functional status in adultswithHB, indicating a reduction in the burden associated with haemophilia.

Simulation of extended half-life replacement FIX therapy dosing to achieve comparable FIX activity to that of fidanacogene elaparvovec gene therapy in haemophilia B patients (PO182, EAHAD 2024)

J.Wojciechowski, P. Gaitonde, L.Wilcox

Introduction: Standard-of-care for severe haemophilia B is prophylactic coagulation factor IX (FIX) replacement therapy [such as eftrenonacog alfa (Alprolix) 50 IU/kg once weekly or 100 IU/kg every 10 days]. Fidanacogene elaparvovec gene therapy (referred as GTx) is a recombinant adeno-associated virus vector carrying the gene that encodes for a high activity variant of human FIX. The objectives were to determine the dose and frequency of FIX prophylaxis (using Alprolix as the example) required to maintain trough FIX activity at levels predicted for GTx up to 25 years.
Methods: A previously developed longitudinal pharmacometrics model of FIX activity (Actin FSL one-stage assay) following GTx administration was used as a reference response for 25 years. FIX activity following Alprolix dosing was simulated for 500 virtual individuals using a published population pharmacokinetic model.1 At each year for 25 years, the dose (fixed once weekly) and frequency (fixed 50 IU/kg) required to achieve trough FIX activity comparable to the time-matched mean GTx response was determined for each individual.

Results: The mean GTx response at Years 1, 5, 10 and 25 were 15.3, 11.2, 8.12 and 4.40 IU/dL, respectively. The median [90% prediction interval (PI)] Alprolix dose required to maintain trough FIX activity at the reference during Years 1, 5, 10 and 25 were 251 (145, 493), 174 (101, 342), 117 (67.8, 230) and 47.8 (27.7, 94.0) IU/kg, respectively. The median (90% PI) cumulative dose required in the first 1, 5, 10 and25 years was 13,047 (7546, 25,653), 54,494 (31,516, 107,147), 90,088 (52,104, 177,134) and 146,630 (84,804,288,302) IU/kg, respectively. The median (90% PI) frequency required during Years 1, 5, 10 and 25 were every 2.72 (2.06, 3.56), 3.42 (2.54, 4.51), 4.35 (3.23, 5.84) and 7.18 (5.24, 9.72) days, respectively.

Discussion/Conclusion: The simulated Alprolix doses and frequencies required to maintain reference FIX activity levels comparable to GTx exceeded 100 IU/kg once weekly and 50 IU/kg once weekly in the first 10 years. These are conservative estimates as additional doses might be needed for on-demand treatment of bleeds. This reinforces that GTx results in FIX activity not achievable within the labelled posology for Alprolix.

BE-101

Development of BE-101, an autologous ex vivo precision gene engineered B cell medicine that produces active and sustained levels of factor IX for the treatment of haemophilia B (OC 11.3, ISTH 2024)

Wing Yen Wong et al

Background: Despite advances in treatment options for haemophilia B, significant unmet needs remain, notably disease and treatment burden.

Aims: Terminally differentiated human plasma cells derived from genetically engineered B Cell Medicines (BCMs), potentially offer natural longevity (average half-life up to 17 years), capacity for high levels of protein secretion, ability to engraft without host preconditioning, and re-dosability, thus makes them an attractive platform to provide durable and long-lasting effects in adolescents and children as well as adults.

Methods: In this study, primary human B cells were isolated, activated, and engineered by CRISPR/Cas9 genome editing followed by AAV-mediated homology directed repair insertion of human F9 gene into the C-C chemokine receptor type

5 (CCR5) safe harbor locus. The cells were then further expanded and differentiated towards the plasma cell lineage, resulting in FIX-producing BCMs.

Results: Engineered BCMs secreted up to 60 ng/1e6 cells/hour of FIX protein. BCM-produced FIX analysed by LC-MS demonstrated gamma-carboxylation of FIX protein Gal-domain. Vitamin K-dependent activated partial thromboplastin time (aPTT) using the one-stage clotting and immunocapture chromogenic assays (left Figure), were employed to verify the biological activity of BCM-produced FIX. FIX-expressing BCMs were transferred into immunodeficient NOG-hIL6 mice, with FIX production demonstrated at least 168 days (right Figure). There were no FIX-producing BCMs-related safety findings. GLP toxicology and off- target evaluation studies are ongoing with no concerns identified to date.

Conclusion(s): In summary, we have developed an ex vivo precision gene-engineered B cell medicine that produces active and sustained levels of FIX for the treatment of haemophilia B (BE-101). We are rapidly moving toward clinical application and in anticipation of the first-in-human clinical trial in 2024 for people with moderately severe to severe haemophilia B.

Bypassing Agents

Phase 1a Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Single Ascending Doses of Intravenous TU7710 in Warfarin Pretreated Healthy Male Subjects (PB0509, ISTH 2024)

Byungwook Kim et al

Background: TU7710 is a novel recombinant fusion protein linking activated FVII with human transferrin (rVIIa-TF). In nonclinical studies, TU7710 exhibited hemostatic effects and a prolonged half-life. It is in development as an on-demand treatment for haemophilia patients with inhibitors.

Aims: TUB4PI-01 study (NCT06025552) is aimed to assess the pharmacokinetics (PK), pharmacodynamics (PD), and safety of single ascending doses of intravenous TU7710 in warfarin pretreated healthy male subjects.

Methods: In a double-blind, placebo-controlled, single ascending dose design, 5 dose levels (100, 200, 400, 800 µg/kg, last dose to be determined) will be investigated, with 8 healthy subjects per cohort randomized to receive either TU7710 or placebo in 6:2 ratio. Before TU7710 treatment, subjects underwent 8-day warfarin pretreatment to achieve a steady-state INR level ranging from 2.00 to 3.00. A single IV dose of TU7710 or placebo was administered. Warfarin administration was continued for 4 days post-administration. Plasma FVIIa activity (PK), INR (PD), and safety profiles were assessed. Anti-drug antibodies will be assessed. Informed consent and ethics committee approval were obtained.

Results: Cohort 1 (100 µg/kg) and Cohort 2 (200 µg/kg) have been completed, while Cohort 3 to 5 is currently ongoing. Following TU7710 dosing, a significant increase in plasma FVIIa activity was observed in 6 PK data from each Cohort. The average mean residence times (MRTs) were 6.15 and 7.47 hours; the median terminal half-life was 13.80 and 12.39 hours; and the mean maximum plasma FVIIa activity (Cmax) was 8.62 and 13.46 IU/mL for Cohort 1 and 2, respectively (Table 1). A marked decrease in INR was observed after TU7710 administration (Figure 1). All adverse events were of mild intensity.

Conclusion(s): TU7710 displayed a prolonged half-life and successfully achieved normal INR levels in healthy subjects pre-treated with warfarin. This data provides support for the potential application of TU7710 in the treatment of haemophilia patients with inhibitors.

An Open-label, Dose-Escalation, Multicenter Phase I Study to Evaluate the Safety, Immunogenicity, and Pharmacokinetics/pharmacodynamics (PK/PD) of Single Dose SS109 in Haemophilia A/B patients with Inhibitor (OC 21.5, ISTH 2024)

Mankai Ju et al

Background: Bleeding episodes (BEs) in haemophilia patients with inhibitors require the administration of bypassing agents such as activated recombinant human factor VII (rhFVIIa). SS109 is a long-acting rhFVIIa-Fc fusion protein. Nonclinical studies showed that the hemostasis of SS109 is better than that of NovoSeven® in the same dose, and the half-life is 2.5 times longer than that of NovoSeven® in cynomolgus monkeys.

Aims: To evaluate the safety, immunogenicity, and PK/PD characteristics of single-dose SS109 in haemophilia (FVIII activity ≤1% or FIX activity ≤2%) patients with inhibitors.

Methods: In this first-in-human, open-label, dose-escalation, multi-center study, 27 male patients aged 18-65 years were enrolled. Five doses of SS109 (30, 60, 120, 240, and 360 μg/kg) were examined, and the safety, immunogenicity, and PK/PD were evaluated. This study received approval by each site's IEC/IRB and written informed consents were obtained from all patients.

Results: Single dose of SS109 at all 5 doses was well-tolerated. Two adverse events occurred in 2 patients (7.4%) were possibly related to SS109. No hypersensitivity or allergic reactions occurred. Table 1 summarises the baseline-corrected FVII activity PK parameters of SS109. Both the Cmax and the AUC were dose-dependent across 5-dose level, with linear dose proportionality being observed within the dose range from 120 to 360μg/kg (Figure 1). The mean half-life ranged from 9.5 hours to14.5 hours, 3 to 7-fold longer than that of NovoSeven®. The aPTT and PT in patients were immediately shortened but returned to the baseline level around 24h and between 48h and 72h, respectively. The maximum reduction (ΔEmax) of PT and aPTT after SS109 administration are shown in Table 1.

Conclusion(s): This study demonstrated that SS109, a long-acting rhFVIIa-Fc, was well-tolerated and had dose-dependent PK/PD characteristics that support further assessment of its potential haemostasis efficacy in BEs in haemophilia patients with inhibitors.

Rebalancing Agents

Concizumab (brand name Alhemo)

Concizumab efficacy results at 56-week cut-off in patients with haemophilia A/B without inhibitors: an intra-patient analysis from the phase 3 explorer8 study (OC 40.4, ISTH 2024)

Anthony Chan et al

Background: Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development as a once-daily subcutaneous prophylaxis for patients with haemophilia A/B (HA/HB) with and without inhibitors. Intra-patient efficacy of concizumab compared with previous prophylaxis was evaluated in a subset of patients; confirmatory analysis results have been reported (Chowdary P, OC59.1. RPTH. 2023:7[Suppl 2]).

Aims: To present descriptive statistics of efficacy at the 56-week cut-off for a subset of patients with HA/HB without inhibitors on concizumab prophylaxis in explorer8 (NCT04082429), and descriptive statistics for the same patients while on stable factor prophylaxis in a prior non-interventional study (explorer6; NCT03741881).

Methods: Male patients (≥12 years) were assigned to one of four arms in explorer8. Descriptive statistics on the number of treated spontaneous and traumatic bleeding episodes at the 56-week data cut-off were assessed in a subset

of patients receiving concizumab in a non-randomized arm of explorer8 and also in the same patients while previously on stable factor prophylaxis for ≥24 weeks in explorer6. Stable factor prophylaxis was defined as the time after an initial period on prophylaxis of ≥24 weeks. The 56-week cut- off was defined as when all patients in concizumab arms had completed their 56-week visit or permanently discontinued treatment.

Results: Descriptive assessments for treated spontaneous and traumatic bleeding episodes are presented by haemophilia subtype (Table 1): for patients with HA, median annualised bleeding rate (ABR) (interquartile range [IQR]) was 2.2 (0.8–6.2) on previous factor prophylaxis and 1.7 (0.5–4.8) on concizumab at the 56-week cut-off; for patients with HB, median ABR (IQR) was 2.1 (0.9–4.2) on previous prophylaxis and 1.3 (0.0–6.4) on concizumab at the 56-week cut-off.

Conclusion(s): Low median ABRs for treated spontaneous and traumatic bleeding episodes were maintained at the 56-week cut-off, consistent with 32-week cut-off results, in patients with HA/HB without inhibitors, previously on stable factor prophylaxis.

Efficacy and safety of concizumab prophylaxis in haemophilia A or B with and without inhibitors: 56- week cut-off results of the phase 3 explorer7 and explorer8 studies (OR07, EAHAD 2024)

J. Windyga et al

Introduction: Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development as a once-daily subcutaneous prophylaxis for haemophilia A/B with and without inhibitors (HAwI/HBwI and HA/HB). The efficacy and safety of concizumab in patients with HAwI/HBwI and HA/HB were assessed in the phase 3 explorer7 (NCT04083781) and explorer8 (NCT04082429) trials, respectively. Primary and confirmatory analysis cut-off (32-week) results were previously presented; 56-week cut-off results are shown here.

Methods: Male patients (≥12 years) with HAwI/HBwI and HA/HB comprised the four arms of the trials. Arm 1 received concizumab after 24 weeks of on-demand treatment; arms 2−4 received concizumab from the study onset. The dosing regimen consisted of a 1.0 mg/kg loading dose (Day 1), then a daily dose of
0.20 mg/kg (Day 2+), with potential adjustment to 0.15 or 0.25 mg/kg based on concizumab plasma concentration after 4 weeks. The 56-week cut-off was defined as when all patients in concizumab arms 2−4 had completed a 56-week visit or permanently discontinued treatment. Bleeding episodes were analysed using the full analysis set of patients (arms 1−4) on treatment, excluding periods on ancillary therapy, from the start of the new concizumab dosing regimen until the 56-week cut-off (explorer7/explorer8), or on the initial concizumab dosing regimen for patients not exposed to the new dosing regimen (explorer7).

Results: The 56-week cut-off analyses of bleeding episodes comprised patients in arms 1−4 exposed to concizumab (i.e., including patients from arm 1 who switched to concizumab prophylaxis after 24 weeks of on-demand treatment). It contained 76 patients with HAwI, 51 patients with HBwI (explorer7), 80 patients with HA, and 64 patients with HB (explorer8). Median annualised bleeding rate (interquartile range) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis was 0.7 (0.0−3.0) for HAwI, 1.1 (0.0−3.2) for HBwI, 1.7 (0.0–4.5) for HA, and 2.8 (0.0–6.4) for HB. No thromboembolic events were reported from restart of the trials until the 56-week cut-off of either trial.

Discussion/Conclusion: Concizumab-exposed patients maintained a low bleeding rate with a favourable safety profile after >1 year of exposure.

Surgical procedures and haemostatic outcome in patients with haemophilia receiving concizumab prophylaxis during the phase 3 explorer7 and explorer8 trials (PO064, EAHAD 2024)

F.-J. Lopez-Jaime et al

Introduction: Concizumab is an anti-tissue factor pathway inhibitor monoclonal antibody antibody in development as once-daily subcutaneous prophylactic treatment for haemophilia of all subtypes. The phase 3 explorer7 (NCT04083781) and explorer8 (NCT04082429) trials investigated the efficacy and safety of concizumab prophylaxis (PPX) in patients with haemophilia A or B with (HAwI/HBwI) or without (HA/HB) inhibitors. Minor surgical procedures performed at the 56-week cut-off are summarised.

Methods: Patients in explorer7 and explorer8 trials were exposed to no PPX (arm1) or concizumab PPX (arms2–4) based on their treatment regimen before the trial. After the main part of the trial, all patients could continue in the extension part receiving concizumab for up to 136 weeks. Informed consent/ethics committee approval was obtained. Minor surgical procedures were permitted. Planned major surgery was not permitted, a concizumab pause was advised for acute major surgery. Surgical procedure data were collected at the 56-week cut-off. Local/topical use of anti-fibrinolytics was permitted during surgical procedures. Patients undergoing minor surgical procedures continued to receive concizumab PPX during the perioperative period with no change to dosage.

Results: In total, 278 patients received concizumab PPX, of these, 30 patients (six adolescents aged 12–17 years and 24 adults aged 18–64 years) underwent minor surgical procedures. Nine patients had HA (30.0%), 10 had HB (33.3%), seven had HAwI (23.3%) and four had HBwI (13.3%). Dental procedures were most frequent (n = 24), other procedures included port removal, colonoscopy, arthrodesis and urethral augmentation. In addition, seven cases of major surgery were reported in two patients with HA, two with HB, one with HAwI and two with HBwI. Minor surgery-related bleeding episodes (n = 15) were reported for 14 of the 38 minor surgical procedures, and eight bleeding episodes were treated. Fourteen of the 15 bleeding episodes were classified as mild/moderate. The median duration of minor surgery-related bleeding was 2 days and the mean number of injections with factor products required to treat these bleeds was 1.5 (SD 0.8).

Discussion/Conclusion: Minor surgical procedures were undergone safely in patients with haemophilia on concizumab PPX during the phase 3 explorer7 and explorer8 trials. Except for one, all surgical-related bleeding episodes were mild or moderate.

Management of breakthrough bleeding episodes in the phase 3 concizumab studies (OC 40.5, ISTH 2024)

Johnny Mahlangu et al

Background: Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development as a once-daily subcutaneous prophylaxis for haemophilia A/B with inhibitors (HAwI/HBwI; explorer7 [NCT04083781]) and without inhibitors (HA/HB; explorer8 [NCT04082429]). Spontaneous or traumatic breakthrough bleeding (BTB) can occur in patients with haemophilia who are treated prophylactically; guidance for the management of these events should be considered.

Aims: To investigate BTB management from the phase 3 explorer7 and explorer8 56-week data.

Methods: In the phase 3 concizumab studies, bleeding episodes were reported along with the hemostatic treatment used to manage the bleed. Guidance for managing mild/moderate BTBs was included in these studies, generally using the lowest dose of the required treatment, according to local labeling. Classification of BTB severity was the responsibility of the investigator.

Results: At the 56-week cut-off, BTBs that occurred in patients receiving concizumab were most frequently in joints,

occurred spontaneously, and were reported as mild/moderate in severity (Table 1). Most BTBs of mild/moderate severity were treated with one injection of the respective BTB treatment (Table 2). In people with HAwI/HBwI, bleeds were most often managed with recombinant activated factor VII (median consumption per injection: mild/moderate bleeds in HAwI 90.0 µg/kg and HBwI 90.0 µg/kg; severe bleeds in HAwI 82.0 µg/kg and HBwI 68.0 µg/kg). In people with HA, bleeds were managed with factor VIII (median consumption per injection: mild/moderate bleeds 20.0 IU/kg; severe bleeds 20.9 IU/kg) and in people with HB with factor IX (mild/moderate bleeds 30.0 IU/kg; severe bleeds 28.9 IU/kg).

Conclusion(s): BTBs that occurred in patients receiving concizumab prophylaxis were mostly of mild/moderate severity and could be effectively treated in alignment with the trial protocol guidance provided. Most mild/moderate bleeds were resolved with a single injection of factor or bypassing agent.

Marstacimab

Joint health in participants with haemophilia A and haemophilia B without inhibitors treated with marstacimab from the phase 3 basis trial (PO074, EAHAD 2024)

J. Mahlangu et al

Introduction: Marstacimab is an investigational monoclonal antibody targeted to tissue factor pathway inhibitor to improve haemostasis. BASIS (NCT03938792) is an open-label, phase 3 marstacimab trial in participants (pts) with severe (FVIII < 1%) haemophilia A (HA) or moderately severe to severe (FIX ≤2%) haemophilia B (HB) with or without inhibitors. We report joint health data of pts without inhibitors.

Methods: Screened males aged 12–<75 years entered a 6 months observational phase (OP) and received on-demand (OD) or routine prophylaxis (RP) factor replacement. Pts in the 12 months active treatment phase (ATP) received a 300 mg subcutaneous marstacimab loading dose and subsequent 150 mg once/wk. Pts could then enrol in a long-term extension (LTE) study. Joint and target joint bleeds were monitored. Joint health was assessed using the Haemophilia Joint Health Score (HJHS; lower score indicates better joint health).

Results: A total of 128 pts (median age, 30 [range 13–66] years) entered the OP (n: OD: HA 29, HB 8; RP: HA 72, HB 19); 116 (n: OD 33, RP 83) entered the ATP and 87 were treated in the LTE (at time of data cut, n: OD 29, RP 58; duration: 34−483 days). At baseline (BL), 89 pts (69.5%; n: OD 36, RP 53) had ≥1 target joint. Compared with OD, marstacimab reduced the incidence of joint bleeds (32.9 vs. 2.8; p < .0001) and target joint bleeds (23.2 vs. 1.8; p < .0001), with numerical reductions in the LTE (1.9 and 0.9, respectively). HJHS decreased 2.8 points versus OD (p = .3) at 6 months and maintained to d180 of the LTE (mean [SD] change from LTE BL [CFB]; 1.1 [2.5]; n = 19). Mean (SD) number of target joints were lower versus OD (0.2 [0.7] vs. 1.7 [1.4]) and maintained over the LTE (0.07 [0.258]). Compared with RP, marstacimab reduced the incidence of joint bleeds (5.7 vs. 4.1, p = .1680) and target joint bleeds (3.4 vs. 2.5; p = .2811), with numerical reductions in the LTE (1.9 and 0.9, respectively). HJHS decreased 2.0 points versus RP (p = .0835) at 6 months and maintained to d180 of the LTE (mean [SD] CFB, −2.7 [14.3]; n = 24). Mean (SD) number of target joints were similar versus RP (0.3 [0.9] vs. 0.3 [0.7]) and maintained over the LTE (0.1 [0.4]).

Discussion/Conclusion: Marstacimab reduced joint bleeds, HJHS and number of target joints in pts with severe HA or moderately severe to severe HB without inhibitors and with high BL prevalence of target joints versus prior OD or RP. Efficacy of marstacimab was maintained up to 16 months in the LTE.

Fitusiran

Incidence of thrombotic events in the fitusiran clinical development program (OC 40.2, ISTH 2024)

Guy Young et al

Background: Fitusiran, a subcutaneous, investigational siRNA therapeutic lowers antithrombin (AT) with the goal of increasing thrombin generation and rebalancing hemostasis in people with haemophilia (PwH) A or B, regardless of inhibitor status. A revised AT-based dose regimen (AT-DR) targeting AT levels between 15–35% was implemented to mitigate thrombotic risk during clinical development.

Aims: To describe thrombotic events in the fitusiran clinical program that occurred on the AT-DR and the original dose regimen (ODR).

Methods: Analysis included males aged ≥12 years with moderate or severe haemophilia A or B, with or without inhibitors who participated in fitusiran studies ATLAS-INH (NCT03417102), ATLAS-A/B (NCT03417245) and ATLAS-PPX (NCT03549871), ATLAS-OLE (NCT03754790), or Phase I/II OLE (NCT02554773). Integrated safety analysis compared the exposure-adjusted incidence rate (EAIR) of thrombotic events in participants exposed to the fitusiran AT-DR versus the ODR. Informed consent and ethics committee approval were obtained for all studies.

Results: Overall, 286 participants were exposed to fitusiran AT-DR (n=221 haemophilia A [HA]; n=65 haemophilia B [HB]) and 270 were exposed to ODR (n=211 HA; n=59 HB). Three participants had moderate haemophilia; all other participants had severe haemophilia. Total patient-years of exposure were 486.0 (≥12 months exposure n=237) with the AT-DR and 306.8 (≥12 months exposure n=101) with the ODR. There were nine thrombotic events reported in seven participants with the ODR (Table 1), and four events in four participants with the AT-DR (Table 2). Overall, only one thrombotic event, with the ODR, did not have any provoking or significant predisposing risk factors. The EAIR of thrombotic events per 100 patient- years was numerically lower with the AT-DR (0.82) versus the ODR (2.28).

Conclusion(s): The fitusiran AT-DR mitigated the risk of thrombotic events in PwH A or B, irrespective of inhibitor status, compared with the ODR.

Hepatobiliary events in the fitusiran clinical development program with the revised AT-based dose regimen (ISTH, OC 40.3)

Steven Pipe et al

Background: Fitusiran, a subcutaneous, investigational siRNA therapeutic lowers antithrombin with the goal of increasing thrombin generation and rebalancing hemostasis in people with haemophilia (PwH) A or B, regardless of inhibitor status. A revised antithrombin-based dose regimen (AT-DR) was implemented to mitigate risk of adverse events by maintaining AT levels between 15–35%.

Aims: To describe hepatobiliary events in participants who received the fitusiran AT-DR.

Methods: Integrated safety analysis included all males aged ≥12 years with moderate or severe haemophilia A or B, with or without inhibitors who received the fitusiran AT-DR in the following studies: ATLAS-PPX (NCT03549871), ATLAS-OLE (NCT03754790) and a Phase I/II OLE (NCT02554773). Fitusiran dose was individually adjusted to achieve target AT levels of 15–35%. Participants with significant liver disease were ineligible. Informed consent and ethics committee approval were obtained for all studies.

Results: Overall, 286 participants were included in the analysis, with total patient-years of exposure of 486.0 (≥12 months exposure n=237) with the AT-DR. A total of 8/286 (2.8%) and 6/286 (2.1%) participants experienced ALT or

AST elevations >3x upper limit of normal (ULN) with the AT-DR, respectively. The mean (SD) time to elevation was 241 (204.6), and 255 (240.6) days, respectively. All initial ALT/AST elevations >3xULN resolved spontaneously; mean (SD) time to resolution was 55 (26.3) and 45 (11.2) days. One event of asymptomatic transaminase elevation resulted in fitusiran discontinuation at physician discretion. There were no cases of severe liver toxicity or liver failure. Overall, 11/286 (3.8%) participants experienced events of cholecystitis/cholelithiasis, and one participant underwent cholecystectomy. No events of cholecystitis/cholelithiasis resulted in discontinuation of fitusiran.

Conclusion(s): Liver transaminase elevations were infrequent and transient with the fitusiran AT-DR. Events of cholecystitis/cholelithiasis resolved without clinical sequelae and participants continued dosing with fitusiran. The pathophysiological mechanism for these events requires further elucidation and is under investigation.

Surgical experience in people with haemophilia A or B with and without inhibitors receiving fitusiran (OC 14.2, ISTH 2024)

Alok Srivastava et al

Background: Fitusiran, a subcutaneous, investigational siRNA therapeutic lowers antithrombin with the goal of increasing thrombin generation and rebalancing hemostasis in people with haemophilia (PwH) A or B, regardless of inhibitor status. For the management of perioperative hemostasis, Bleed Management Guidelines (BMG) with reduced dose and/or frequency of clotting factor concentrates (CFC) or bypassing agents (BPA) were implemented (Table).

Aims: To describe hemostatic outcomes of major surgeries conducted while on fitusiran prophylaxis in PwHA/B aged ≥12 years, regardless of inhibitor status.

Methods: All major surgeries in the fitusiran clinical development program until June 2023 were evaluated, including participants on the 80 mg QM and revised antithrombin-based dose regimen. Informed consent and ethics committee approval were obtained. Procedures conducted during fitusiran prophylaxis and AT activity < 60% were included. Major surgeries included: opening into major body cavity, operation on a joint, removal of an organ, operative alteration of normal anatomy, crossing of a mesenchymal barrier, dental extraction of molar teeth or ≥3 nonmolar teeth, or tooth implantation. Investigators/surgeon assessed peri-operative hemostatic control based on the ISTH 4-point response scale (excellent/good/moderate/poor).

Results: Sixty major surgeries (24 in inhibitor patients) were performed. In 47 (78.3%) major surgeries, BMG were followed, and reduced doses were used as perioperative prophylaxis. Four major surgeries were conducted without additional CFC/BPA. Hemostatic control on the day of the surgery was rated excellent/good in 30/31 (97%) cases following BMG and 9/10 (90%) cases not following BMG (Figure). ATIII concentrate was used to reverse the pharmacodynamic effect of fitusiran in 7 surgeries with an excellent/good hemostatic outcome. No major treatment-related safety concerns were identified perioperatively. Postoperative thrombosis occurred only when dosing exceeded BMG recommendations in 2 participants.

Conclusion(s): Major surgeries can be safely and effectively conducted during fitusiran prophylaxis when BMG are followed, irrespective of inhibitor status. Reversal of lowered AT is not necessary.

VGA-039, a Protein S-targeting monoclonal antibody, demonstrates in a Phase Ia healthy volunteer trial the potential of subcutaneous weekly or less frequent prophylactic dosing for bleeding disorders (OC 73.3, ISTH 2024)

Christain Schoergenhofer

Background: Non-factor replacement therapies have the potential to rebalance coagulation 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.

Aims: To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending doses (SADs) of intravenous (IV) or subcutaneous (SC) VGA039.

Methods: This is an unevenly randomized (3 VGA039:2 placebo), double-blind, placebo-controlled, first- in-human, phase Ia trial conducted in healthy volunteers aged ≥18 years and approved by the local ethics committee. Informed consent was obtained. The starting IV SAD was less than the 10% effective concentration value for in vivo thrombin generation in NHPs, with dose escalations up to a pre-specified maximum of 1.0 mg/kg in the absence of dose limiting toxicity (DLT). The starting SC SAD was the maximally tolerated/tested IV dose, with continued dose escalations up to 3.0 mg/kg.

Results: To date, a total of 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. Plasma concentrations of VGA039 have increased dose dependently across the IV and SC cohorts (Figure 1). SC bioavailability is ~98%, with drug concentrations of 1.0 mg/kg IV and SC VGA039 converging after 1 week (Figure 2). At higher tested doses, VGA039 increases ex vivo thrombin generation compared to baseline (presented for all cohorts at the meeting).

Conclusion(s): Emerging data suggest VGA039 is well tolerated and increases thrombin generation in healthy volunteers. Drug concentration profiles demonstrate suitability for weekly or less frequent SC prophylactic dosing for various bleeding disorders. Further investigation of VGA039 is underway in VWD patients.

Results of the first-in-human investigation of HMB-001 for prophylactic management of glanzmann thrombasthenia (OR01, ISTH 2024)

S. Sivapalaratnam et al

Introduction: Glanzmann thrombasthenia (GT) is a rare and severe bleeding disorder caused by deficiency of integrin αIIbβ3, a platelet receptor essential for platelet aggregation. People with GT experience debilitating and sometimes life-threatening bleeding episodes. To date, there are no effective prophylactic options. HMB-001 is a bispecific antibody being developed by Hemab Therapeutics to prevent or reduce the frequency of bleeding episodes in patients with GT. HMB-001 works by binding to and accumulating endogenous activated coagulation factor VII (FVIIa) and targeting it to the surface of activated platelets at the site of vascular injury. This increases the activity of FVIIa to levels that are therapeutically effective. Our Phase 1/2 clinical study aims to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of HMB-001 in individuals with GT.

Methods: The ongoing phase 1/2 study is composed of three parts: part A (single ascending dose); part B (multiple ascending dose) and part C (open label extension). The study includes male and female participants aged 18–65 years old, who have a definitive diagnosis of GT.

Results: Participants included in part A of the study received HMB-001 subcutaneously at dose levels of 0.2 mg/kg, 0.5 mg/kg or 1.25 mg/kg, respectively. At the time of the abstract submission, there were no reported treatment-related adverse events. Pharmacodynamic data showed positive proof of mechanism with a dose-dependent increase in factor VII and factor VIIa as well as signs of coagulation activation based on a dose-dependent reduction in prothrombin time. The pharmacokinetic profile indicates a dose- dependent response and is supportive of infrequent, subcutaneous dosing. Further details of safety, tolerability, pharmacodynamics, and pharmacokinetics will be summarized.

Discussion/Conclusion: The initial safety, tolerability, pharmacodynamics and pharmacokinetics results from part A of the phase 1/2 study are encouraging and support the further development of HMB-001 as a potential prophylactic treatment for GT.

Product 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	Chugal	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 AGENTS (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 PHABwl) in Canada, Austrailia, Japan)
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Martascimab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Pfizer	Phase 3
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	Starting Phase 3 registration trial Received FDA Orphan Drug Designation for HB

GENE THERAPIES IN DEVELOPMENT and/or UNDER HTA REVIEW						
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 roxaparvovec (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
Gene Therapy	Haemophilia A	AAV2/8-HLP- FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	Single intravenous infusion	UCL/St. Jude	Phase 1
Gene Therapy	Haemophilia A	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Single intravenous infusion	Expression Therapeutics	Phase 1
Gene Therapy	Haemophilia A for HAwI	SPK-8016	Recombinant AAV composed of a liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette	Single intravenous infusion	Spark	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 bioengeineered human FVIII (ET3) transgene	Single intravenous infusion	ASC Therapeuticsa	Phase 1/2

Gene Therapy	Haemophilia A	CD68-ET3-LVCD34+	CD34+ hematopoietic stem cells transduced with CD68-ET3 Lentiviral vector (encoding human factor VIII gene) is administered by IV infusion following conditioning regimen	Single intravenous infusion	Christian Medical College, Vellore, India	Phase 1
Gene Therapy	Haemophilia B	Fidanacogene elaparvovec (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. and Canada (brand name Hemgenix) **authorisation in Europe, (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

Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Mode of administration	Developer / manufacturer	Development stage
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,	Pre-clinical phase

CELL-BASED THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	Product name(s)	Name(s) of active ingredient	Mode of	Developer /	**Development stage**
Cell-based therapy	Haemophilia A with inhibitors	TI-168	Autologous FVIII TCR-Treg cell therapy	-	Teralmmune 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 & human von Willebrand factor	CSL Behring	Licensed
Replacement VWF plasma-derived	VWD, Haemophilia A	Haemate P®	Human coagulation factor VIII & 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

Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Developer / manufacturer	Development stage
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
Gene Therapy	**Haemophilia B**	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	CSL Behring	Licensed in 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

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