Novel treatments in haemophilia and other bleeding disorders: A periodic EHC Review

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FOREWORD

Welcome to a new edition 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 both 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 medicinal product developments in rare bleeding disorders. The EHC encourages its NMOs to use the information contained in this review at a national level between their patients, health professionals and other relevant 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 concentrates, bypassing agents, mimetics, rebalancing agents and gene therapy.

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

This publication covers recent medical and scientific updates but does not delve into the basic science of rare bleeding disorders and their treatment. To obtain this type of information, we would suggest consulting the EHCucate app (available on iOS App Store 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 online publications from the Congress of the International Society of Hemostasis and Thrombosis (ISTH), held in June 2023, and the American Society of Hematology (ASH) Meeting and Exposition held in December 2023, as well as other industry updates and news in general.

The first section, an **Update on Recent Marketing Authorisations and Indication Expansion**, provides news on regulatory approvals since January 1, 2023.

The second section, **Report Highlights**, summarises very concisely some of the key advances of 2023 in each of the disease areas and product classes.

The third section, **Research Abstracts and Articles**, presents publications from the medical literature. In this newsletter, the research abstracts have been very lightly edited. The full lists of authors, tables and figures have been removed but we provide an Internet link to the original abstracts and articles.

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 Uwe Schlenkrich, EHC volunteer.
- Miguel Crato, EHC President

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

Sincere regards,

Miguel Crato, EHC President

Disclaimer

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

ABBREVIATIONS

> 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 ½ 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 **Altuviiio** in the U.S.), an extended half-life FVIII for the treatment of haemophilia A, was approved by the U.S. FDA in February 2023. It was also approved in Japan in September 2023. The EMA accepted a marketing authorisation application for efanesoctocog alfa in May 2023. See page 23.

Mimetics

The indication for **emicizumab** (brand name **Hemlibra**) was extended in February 2023 by the European Commission to include those people with moderate haemophilia A (FVIII ≥1% and ≤ 5%) with a severe bleeding phenotype.

Rebalancing agents

Concizumab (brand name **Alhemo**), an anti-tissue-factor pathway inhibitor (TFPI), was approved by Health Canada in March 2023 for the treatment of patients 12 years and older with haemophilia B and inhibitors to FIX requiring prophylaxis and in August 2023 for a similar indication in haemophilia A. In July 2023, the Australian Therapeutic Goods Administration approved concizumab for patients with haemophilia B and inhibitors. Concizumab has also received regulatory approval in Japan. In the U.S. the FDA asked Novo Nordisk for additional information in April 2023 about the drug's manufacturing process and the company's system for monitoring and dosing patients to ensure that the treatment is administered correctly. Novo Nordisk submitted an application to the EMA in February 2023.

Marstacimab, another anti-tissue-factor pathway inhibitor was submitted to the EMA and FDA for marketing authorisation for the prophylaxis in patients with haemophilia A or B by Pfizer in October 2023.

Gene therapy for haemophilia A

Valoctocogene roxaparvovec (brand name **Roctavian**) gene therapy was approved by the U.S. FDA in June 2023 for the treatment of adults with severe haemophilia A with no history of inhibitors and no antibodies to adeno-associated virus serotype 5 (AAV5). The European Commission (EC) granted conditional marketing authorisation to Roctavian in August 2022. See page 24 for two-year outcomes of the phase 3 clinical trial.

Roche announced it is moving into a Phase 3 clinical trial with its haemophilia A gene therapy **dirloctogene samoparvovec**, also known as SPK-8011. At the same time, however, Roche announced it is discontinuing the development of another investigational haemophilia A gene therapy called **SPK-8016**, which was targeting patients with inhibitors to FVIII. Roche stated that SPK-8016 "wasn't having the impact that we thought that it was going to have".

Belief BioMed Group (BBM), an industry-leading biotech company in Shanghai focusing on innovative gene therapies, announced the completion of first subject dosing in its registrational clinical trial (CTR20233400) of **BBM-H803**, a gene therapy for haemophilia A, independently developed and produced by Belief BioMed. BBM-H803 is Belief BioMed's first gene therapy for the treatment of haemophilia A and is the company's second product which has obtained IND approval from the Chinese National Medical Products Administration (NMPA). In December 2022, BBM-H803 was granted Orphan Drug Designation (ODD) by the U.S. Food and Drug Administration (FDA).

Gene therapy for haemophilia B

Regeneron has announced that its next-generation approach to gene replacement therapy for hemophilia B will move into clinical trials in 2024. This CRISPR-mediated targeted gene insertion platform expresses wild-type factor IX from the Albumin locus in the liver. Pre-clinical data in mouse and non-human primates has shown robust and durable FIX expression. As the dividing cells carry the gene, there is no dilution, and children may be eligible for therapy.

Etranacogene dezaparvovec (brand name **Hemgenix**) gene therapy for haemophilia B was approved by Health Canada in November 2023 after previous approvals by the FDA and EMA for severe or moderately severe patients. The indication is for adults requiring prophylaxis. A patient blood sample is required for testing for AAV5 neutralizing antibodies. If a patient has AAV5 neutralizing antibodies above a pre-determined threshold, they will not be eligible for treatment with Hemgenix. See page 30 for 3-year results of the HOPE-B phase 3 clinical trial. In draft guidance released in August 2023, the National Institute for Health and Care Excellence (NICE) recommended against Hemgenix reimbursement by England's National Health Service (NHS) after finding uncertainty about the drug's long-term effectiveness.

Fidanacogene elaparvovec (brand name **BEQVEZ**) gene therapy for haemophilia B was approved by Health Canada in December 2023. The indication is for adults with severe or moderately severe haemophilia B requiring prophylaxis. Baseline testing is required. If a patient is positive for AAVRh74var neutralizing antibodies, they will not be eligible for treatment with BEQVEZ. A marketing authorization application with EMA was started in May 2023. See page 32 for 15-month results of the BENEGENE-2 phase 3 clinical trial. In a draft recommendation released in January 2024, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended reimbursement of fidanacogene elaparvovec with conditions, notably a price reduction.

Monoclonal antibodies

Hemab Therapeutics, a clinical-stage biotechnology company developing novel prophylactic therapeutics for serious, underserved bleeding and thrombotic disorders, announced in December 2023 that it has completed Phase 1, the single ascending dose part, and transitioned to Phase 2, the multiple ascending dose part, of its Phase 1/2 clinical study of **HMB-001** in Glanzmann Thrombasthenia (GT). GT is a platelet disorder that causes severe, potentially life-threatening bleeding episodes. The company also announced that the U.S. Food and Drug Administration (FDA) has cleared Hemab's investigational new drug application (IND) for HMB-001 in GT, enabling enrollment in the U.S. Phase 1 of the clinical study was completed in the UK, and Phase 2 will include additional sites in Europe as well as the U.S. In addition, the FDA granted Fast Track designation to HMB-001, emphasizing the seriousness and high unmet need for treatments for GT. The Fast Track program enables Hemab to have more frequent interactions with the FDA to facilitate the development of HMB-001. See page 45.

2 - REPORT HIGHLIGHTS

AN UPDATE ON NOVEL THERAPIES IN HAEMOPHILIA A

Bispecific Monoclonal Antibodies (Including FVIII Mimetics)

Mim8

Researchers concluded that that **Mim8**, a novel factor VIIIa mimetic bispecific antibody under development by Novo Nordisk is suitable as a long-acting FVIIIa-mimetic bispecific antibody for haemophilia A prophylaxis in those both with and without inhibitors. See page 19.

Research at the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre in Milan evaluated the in vitro cross-reactivity of **Mim8** with the anti-emicizumab antibodies (ADAs) in order to verify whether Mim8 could be a potential alternative therapeutic option for patients who can no longer be treated with emicizumab because of ADAs. See page 21.

NXT007

Single subcutaneous doses of **NXT007**, a novel activated coagulation factor VIII-mimetic bispecific monoclonal antibody that assembles with activated coagulation FIX and FX on the platelet membrane surface, were well tolerated without thromboembolic events in healthy volunteers. The long half life, pharmacological effect, and safety supported the study progress moving to the subsequent phases. Evaluation of safety, efficacy, pharmacokinetics, and immunogenicity on multiple dosing, expected to achieve normal levels of coagulation activity in PwHA, is ongoing. See page 19.

Emicizumab (Hemlibra)

Research from India demonstrated that low-dose **emicizumab** prophylaxis in 10 PwHA resulted in significantly reduced ABR, ABJR, treated bleeds and total target joints when compared to low-dose CFC prophylaxis. This was found to be equivalent to standard-dose emicizumab prophylaxis. See page 20.

Garcia et al report real-world data on the effectiveness of **emicizumab** in children with haemophilia A. Clinical trials have shown success in bleed prevention with emicizumab, but a retrospective chart review of pediatric male patients on emicizumab prophylaxis (n=37) at the Children's Medical Center in Dallas, Texas highlights that serious bleeds, both provoked and unprovoked, can occur in pediatric persons with severe haemophilia A. Up-titration of emicizumab or factor VIII replacement needs consideration in persons with haemophilia with suboptimal bleeding control or who participate in activities categorized as moderate to high risk. See page 22.

Research results suggest that **emicizumab** prophylaxis prevents bleeding in patients with acquired haemophilia A and that immunosuppressive therapy can be deferred while patients are receiving this treatment. See page 20.

Cedric Hermans and Glenn Pierce write that preventive subcutaneous treatment of severe haemophilia A with **bispecific antibodies** that mimic the action of coagulation factor VIII (FVIII) is emerging as an effective alternative to replacement therapy with intravenous administration of FVIII concentrates, and that emicizumab and other FVIII mimetic bispecific antibodies under development should become a part of the WHO Essential Medicines Program as a class for the treatment of severe haemophilia A. Priority should be given to children and all patients with FVIII inhibitors to minimize joint damage and comorbidities, respectively. See page 21.

Factor Replacement Therapies

Efanesoctocog alfa

The XTEND-1 study concluded that in 133 patients with severe haemophilia A, once-weekly **efanesoctocog alfa** (brand name **Altuviiio**) provided superior bleeding prevention to pre-study prophylaxis, normal to near-normal factor VIII activity, and improvements in physical health, pain, and joint health. See page 23. The XTENDKIDS study concluded that once-weekly efanesoctocog alfa was well tolerated and provided highly effective bleed protection and treatment in children with severe haemophilia A. High sustained factor activity was within normal to near-normal levels (>40%) for 3 days and at ~10% at Day 7. See page 23.

Adeno-Associated Virus Gene Therapy

Valoctocogene roxaparvovec

Phase 3 study data of **valoctocogene roxaparvovec** (brand name **Roctavian**) gene therapy in 134 PwHA show the durability of factor VIII activity, with a model-estimated typical half-life of the transgene-derived factor VIII production system of 123 weeks (2 years and 5 months) (95% confidence interval, 84 to 232 weeks), bleeding reduction and positive safety profile at least 2 years after the gene transfer. A total of 106 participants (79.1%) received glucocorticoids in accordance with the protocol. The median time to initiation of glucocorticoid treatment was 8.1 weeks, and the median treatment duration was 230 days (range, 22 to 551). Models of the risk of joint bleeding suggest that the relationship between transgene-derived factor VIII activity and bleeding episodes is similar to that reported for persons with mild-to-moderate haemophilia A. See page 24.

Giroctocogene fitelparvovec

Data from the Phase 1/2 Alta study showed that a single infusion of **giroctocogene fitelparvovec** gene therapy in participants with severe haemophilia A remains generally well tolerated over a period of nearly 4 years post infusion, without sustained AEs and with no AEs associated with increased liver function tests since week 59. Of the 5 participants in the high-dose cohort, 2 had data available through Week 208 and FVIII activity was maintained in the mild to normal range. See page 25.

Dirloctogene samoparvovec

Data from the Phase 1/2 study of **dirloctogene samoparvovec** (previously SPK-8011) showed the therapy increased FVIII activity in 21 of 23 patients. The two exceptions were patients who had experienced an immune reaction against the viral vector. In the 21 patients who experienced an increase in FVIII activity, average annual bleeding rates decreased by more than 90% after up to five years of follow-up. Roche announced it is moving into a phase 3 clinical trial. See page 27.

Factor Replacement Therapies

Sub-cutaneous injection of FIX

Factor IX inhibitor formation is the most serious complication of replacement therapy in haemophilia B. It is exacerbated by severe allergic reactions occurring in up to 60% of patients with inhibitors. Low success rates of immune tolerance induction therapy in haemophilia B necessitate the search for novel immune tolerance therapies; however, this research shows that intradermal (sub-cutaneous) FIX administration is highly immunogenic, suggesting that the skin compartment is not amenable to immune tolerance induction or therapeutic delivery of clotting factors. See page 29.

Gene Therapy

scAAV2/8-LP1-hFIXco Adeno-associated virus gene therapy

Long-term follow-up of the Phase 1 first-in-human gene therapy trial in 10 PwHB has shown expression of transgenic FIX has remained stable over a period of 10 years following administration of scAAV2/8-LP1-hFIXco adeno-associated virus gene therapy. This has resulted in sustained clinical benefit, with substantial reduction in ABR and FIX concentrate use. See page 29.

Etranacogene dezaparvovec

Long-term follow-up during the HOPE-B trial has shown that a single dose of **etranacogene dezaparvovec** (brand name **Hemgenix**) resulted in endogenous FIX Padua expression for over three years. This has resulted in superior bleeding protection compared to FIX prophylaxis in participants without or with AAV NAb titer ≤1:678, and a favourable safety profile. The mean±SD (median; range) endogenous FIX activity of the 54 participants was sustained at 38.6 IU/dL ±17.8 (36.0; 4.8-80.3, n=48) at year 3. See page 30. Of note, the majority of HOPE-B trial participants had a history of chronic HCV and/or HBV infection without active viral disease or evident pre-existing liver fibrosis, with, safety and efficacy observed in these participants. Nine of the 54 participants (17%) received and subsequently discontinued glucocorticoid treatment for elevations in liver aminotransferase levels. See pages 30-32.

Fidanacogene elaparvovec

In the phase 3 BENEGENE-2 study, **fidanacogene elaparvovec** (brand name **BEQVEZ**) yielded endogenous FIX expression in participants with moderately severe to severe haemophilia B, with a significant decrease in bleeding and was generally well tolerated. Mean FIX activity was 27.5% at month 15 and remained stable at month 24. However, 6 of the 45 participants initially responded to therapy before a heterogenous decline in FIX activity was seen and returned to FIX replacement therapy. Twenty-eight of the 45 participants (62%) received corticosteroids for presumed immune response. See pages 32-34.

An Update on Bypassing Agents

The pivotal phase 3 PERSEPT 1 trial of **eptacog beta** (brand name **CEVENFACTA**), a recombinant human activated Factor VIIa (rhFVIIa) concentrate included 27 persons with haemophilia A or B with inhibitors (PwHABI). Participants were aged ≥12 years and subcategorized based on weight: underweight, normal weight, or overweight/obese. Increased efficacy was achieved at 12 hours with the 225 µg/kg initial dose regimen (IDR) over the 75 µg/kg IDR, in the normal weight and overweight/obese groups. At 24 hours post-initial eptacog beta, nearly all BEs in each BMI group were successfully treated. Eptacog beta was well tolerated in subjects across all BMI groups. No thromboembolic events were reported. With the high efficacy seen at 24 hours, eptacog beta offers an important treatment option for PwHABI of all BMI classes. See page 34.

An Update on Rebalancing Agents

Concizumab is an anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibody. Research assessed the safety and efficacy of **concizumab** (brand name **Alhemo**) prophylaxis (PPX) and compared physical activity and health economics in patients with HA and HB with inhibitors (HAwI, HBwI) on PPX vs no PPX. The authors concluded that daily treatment of HAwI/HBwI with concizumab PPX effectively reduced bleeding episodes compared with no PPX, and concizumab was considered safe and well tolerated. An increased percentage of awake time was spent in moderate and moderate-to-vigorous physical activity, and there was no significant difference in health economic parameters in patients on concizumab PPX vs no PPX. In a second study, in 148 patients with HA and HB without inhibitors**,** concizumab prophylaxis showed efficacy in adult and adolescent patients with HA/HB at the 56-week cut-off with a median ABR of 1.7. Concizumab prophylaxis was considered safe and well tolerated in patients with HA/HB. No thromboembolic events were reported. See pages 35-38.

Marstacimab is an anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibody. Efficacy and safety of **marstacimab** in 116 participants with severe HA or moderately severe to severe HB without inhibitors was compared with previous factor replacement therapy in the phase 3 Basis trial. Compared with previous OD or RP therapy, once weekly subcutaneous marstacimab was safe and effective for reducing bleeding events in participants with severe HA or moderately severe to severe HB without inhibitors beyond 12 months in the phase 3 study and up to an additional 16 months in the LTE study. Mean (95% CI) ABR for treated bleeds was reduced for on-demand (OD) (91.6% [88.1–94.1%]) and for routine prophylaxis (RP) (35.2% [5.6–55.6%]) participants over the 12-month ATP and marstacimab demonstrated superiority vs OD (P<0.001) and non-inferiority and superiority vs RP (P=0.0376) therapy. No deaths or thromboembolic events were recorded in the phase 3 study or the LTE. See pages 38-41.

Fitusiran is a subcutaneously administered small interfering RNA therapeutic that targets antithrombin (AT). The pharmacokinetics (PK) / pharmacodynamics (PD) of fitusiran prophylaxis (changes in AT and peak thrombin generation, TG), were reported from three Phase 3 trials—ATLAS-INH, ATLAS-A/B and ATLAS PPX—in 187 PwH A or B, with or without inhibitors. The primary endpoint for all trials was annualized bleeding rate (ABR). Exploratory endpoints included change in AT levels and peak TG over time, both of which were assessed at monthly intervals. Safety and tolerability were also assessed. The authors

concluded that monthly 80 mg fitusiran prophylaxis met the target pharmacodynamic effect of AT lowering and increased peak TG by Day 29 in PwH A or B, with or without inhibitors. These findings and low ABRs suggest fitusiran has the potential to rebalance haemostasis and provide sustained bleed protection in PwH A or B, irrespective of inhibitor status.

An updated **fitusiran** population PK/PD (PopPK/PD) model used pooled Phase 1/2 and Phase 3 AT activity data to guide an AT-based dose regimen for Phase 3 trials in adults with haemophilia. Authors concluded that the PopPK/PD model simulations confirm that the fitusiran AT-based dose regimen with a starting dose of 50 mg Q2M that can be escalated or de-escalated maintains the target AT range of 15–35% in the majority of PwH. It is predicted approximately 88% of PwH will require zero or one dose change. The efficacy and safety of the fitusiran AT-based dose regimen is being evaluated in ongoing clinical trials. See pages 41-43.

AN UPDATE ON NOVEL THERAPIES IN VON WILLEBRAND DISEASE AND OTHER RARE BLEEDING DISORDERS

Rondoraptivon pegol (BT200) is a pegylated aptamer binding to the A1 domain of VWF to enhance VWF/factor VIII (FVIII) levels by decreasing their clearance. Researchers are studying the potential benefit of rondoraptivon pegol, a pegylated aptamer, in patients with type 2B VWD in a prospective phase 2 trial. Rondoraptivon pegol rapidly tripled platelet counts and increased circulating VWF antigen, which doubled FVIII activity levels. VWF ristocetin cofactor and VWF collagen-binding activity increased, and HMW multimers appeared. These pronounced improvements reversed during the washout period of the drug, thus demonstrating causality. The aptamer directly corrects the underlying defect of type 2B VWD, thus providing a novel potential option for prophylaxis and treatment of patients with this VWD type. These data provide the basis for a phase 2b/3 trial in such patients. See page 44.

In July 2023, Sanofi announced a study to characterize the pharmacokinetics (PK) of **BIVV001** (**efanesoctocog alfa**, brand name **Altuviiio**) after a single intravenous (IV) administration, and to assess the safety and tolerability of a single IV dose of BIVV001 in adult patients with types 2N and 3 VWD. Eligibility criteria include von Willebrand disease (VWD), age between 18 and 65 years, male or female. See page 44.

In April 2023, Vega Therapeutics announced a clinical trial to assess VGA039, an anti-protein S monoclonal antibody, in the treatment of von Willebrand disease (VWD). The trial has been designed to evaluate the tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and safety of VGA039 after a single IV or SC dose administration in healthy participants and single SC dose administration in VWD patients. See page 44.

3 - RESEARCH ABSTRACTS AND ARTICLES

HAEMOPHILIA A

Mimetics And Other Non-Replacement Therapies

Mim8, a Novel Factor VIIIa Mimetic Bispecific Antibody, Shows Favourable Safety and Pharmacokinetics in Healthy Adults

https://www.rpthjournal.org/article/S2475-0379(23)00233-9/fulltext

J Thromb Haemost. 2023 Dec 22:S1538-7836(23)00914-5. doi: 10.1016/j.jtha.2023.12.016. Epub ahead of print. PMID: 38142846.

Introduction: The FRONTIER1 (NCT04204408, NN7769-4513) single ascending dose and the 4882 pharmacokinetic (PK) studies (NCT05127473, NN7769-4882) examined the safety, tolerability, PK, and pharmacodynamics (PD) of Mim8 in healthy adult males. **Mim8 (denecimig)** is a novel activated coagulation factor VIII-mimetic bispecific antibody that assembles with activated coagulation FIX and FX on the platelet membrane surface. **Methods:** The FRONTIER1 single ascending dose study consisted of 6 cohorts, each with 6 participants who received a single subcutaneous (s.c.) dose of Mim8 and 2 participants who received a placebo. The 4882 PK study had 11 arms, each with 6 participants who received a single s.c. dose of Mim8. The primary endpoint for both studies was treatment-emergent adverse events. Other safety assessments included relative changes in D-dimer, prothrombin fragments 1 and 2, fibrinogen, and platelets. The PK and PD were assessed using Mim8 plasma concentration and activated partial thromboplastin clotting time and thrombin generation, respectively. **Results**: Mim8 was well tolerated, and there were no severe treatment-emergent adverse events. The PK properties of Mim8 in both studies were consistent with dose-proportionality. The terminal half-life of Mim8 after a single dose was approximately 1 month, and maximum plasma concentration was reached after 10 days. **Conclusion:** The PK and PD profiles suggest that Mim8 is suitable as a long-acting FVIIIa-mimetic bispecific antibody for haemophilia A prophylaxis.

Safety, Pharmacokinetics, and Pharmacodynamics of Single Subcutaneous Injection of NXT007, an Emicizumab-Based Next-Generation Bispecific Antibody, in Healthy Volunteers (NXTAGE Study)

https://doi.org/10.1016/j.rpth.2023.100465

Introduction: In a late-breakthrough oral presentation at ISTH and abstract published in Research and Practice in Thrombosis and Haemostasis in October 2023, Shima et al evaluated the safety, pharmacokinetics, and pharmacodynamics of **NXT007** in health volunteers (HVs). NXT007 is a bispecific antibody that mimics the cofactor function of activated factor VIII and was engineered and optimized based on emicizumab. Nonclinical investigations suggested its potential to provide non-haemophilic level of coagulation activity to people with haemophilia A (PwHA). A phase I/II clinical study of NXT007 in healthy volunteers (HVs) and PwHA is currently ongoing (NXTAGE; JapicCTI-194919). **Methods**: Forty Japanese male HVs were enrolled in Part A of NXTAGE which consisted of five cohorts. In each cohort,

eight subjects were randomized to receive a single injection of NXT007 (N = 6; 0.0018, 0.0054, 0.018, 0.054, or 0.18 mg/kg) or placebo (N =2) subcutaneously under a blinded condition. Informed consent and ethics committee approval were obtained. **Results**: NXT007 exposure increased dose-dependently. Mean elimination half-life was approximately 10 weeks in anti-NXT007 antibody (ADA)-negative subjects. With ex vivo neutralization of endogenous factor VIII in plasma samples, activated partial thromboplastin time was shortened and thrombin generation was promoted in a dose-dependent manner. The incidence of adverse events (AEs) was comparable between the overall NXT007 groups (17 of 30 subjects, 56.7%) and the placebo groups (6 of 10 subjects, 60.0%). There were no dose-dependent increases in the incidence of AEs and no thromboembolic events. One SAE of erythema whose causality to NXT007 could not be ruled out was reported in the 0.0054 mg/kg group. Nine subjects developed ADAs; all of them were considered associated with faster clearance of NXT007 with no impact on safety. **Conclusion(s**): Single subcutaneous doses of NXT007 were well tolerated without thromboembolic events. The long half-life, pharmacological effect, and safety supported the study progress to the subsequent parts. Evaluation of safety, efficacy, pharmacokinetics, and immunogenicity on multiple dosing expected to achieve non-haemophilic level of coagulation activity in PwHA is ongoing.

Low-Dose Emicizumab Prophylaxis in Severe Haemophilia a Patients – A Pilot Study with a Much Anticipated Promise for a Resource Limited Country

https://www.rpthjournal.org/article/S2475-0379(23)04166-3/pdf

J Thromb Haemost. 2023 Dec 30:S1538-7836(23)00925-X. doi: 10.1016/j.jtha.2023.12.023. Epub ahead of print. PMID: 38160726.

Introduction: Patil et al assessed the efficacy of low-dose emicizumab prophylaxis (3 mg/kg monthly) in comparison to standard-dose emicizumab and low-dose FVIII prophylaxis (10–20 IU/kg twice a week) and compared the cost of these treatments. Prophylaxis is the standard-of-care for persons with haemophilia (PwH) reducing ABR from 8 to 15 to 0–1. However, only 4–9% PwH are on prophylaxis in India. Low-dose CFC prophylaxis has been studied in China, India, Tunisia, etc. showing significant reduction in ABR from 7 to 0.5. However, long term outcomes of low-dose prophylaxis showed average ABR and target joints were persistent. Emicizumab prophylaxis has shown an excellent efficacy in HAVEN1-4 studies. However, a majority of the PwH in developing countries do not have access to emicizumab due to very high cost. **Methods**: A total of 10 PWH (age:3.5–12 yrs); 5 with inhibitors (4–15 BU/ ml) were initiated on low-dose emicizumab prophylaxis; 4 PWH on standard-dose emicizumab prophylaxis and 10 PWH on low-dose CFC prophylaxis. Number of bleeds, joint-bleeds, treated-bleeds, target-joints & HJHS joint score were documented; clotting profile was assessed by Non-Activated Thromboelastometry (NATEM-ROTEM). Trough blood plasma EC-levels were assessed by modified one-stage factor assay using r2diagnostic EC calibrator/controls. **Results**: ABR, ABJR, treated-bleeds and total target-joints were found significantly reduced ($p < 0.0001$, 95% CI) when compared to low-dose CFC prophylaxis and equivalent to standard-dose emicizumab prophylaxis. Improvements in HJHS were observed in patients on low-dose and standard-dose emicizumab prophylaxis. Clotting-time and clot-formation time of low-dose emicizumab prophylaxis group was significantly shortened compared to low-dose CFC prophylaxis group ($p < 0.0001$,95%CI), and almost equivalent to standard-dose EC prophylaxis. Trough blood plasma EC levels was stable at 50 µg/ml and 26 µg/ml in PWH on standard-dose and low-dose emicizumab respectively.

Emicizumab Prophylaxis Instead of Immunosuppressive Therapy in Patients with Acquired Haemophilia A (AHA)

https://doi.org/10.1016/j.rpth.2023.100289

Lancet Haematol. 2023 Nov;10(11):e913-e921. doi: 10.1016/S2352-3026(23)00280-6. Epub 2023 Oct 16. PMID: 37858328.

Introduction: In a late-breakthrough oral presentation at ISTH and abstract published in Research and Practice in Thrombosis and Haemostasis in October 2023, Tiede et al evaluated the efficacy and safety of emicizumab in AHA patients not treated with immunosuppressive therapy (IST). IST is associated with adverse events and mortality in patients with acquired haemophilia A (AHA). This study aimed to assess whether patients can be treated with emicizumab prophylaxis instead of IST. **Methods**: This open-label, non-randomized clinical trial enrolled patients with AHA who had not received IST before enrollment. Patients received accelerated subcutaneous emicizumab loading on day 1 (6 mg/kg) and day 2 (3 mg/kg), followed by 1.5 mg/kg weekly until week 12. The primary endpoint was the mean rate of clinically relevant bleeds per patient-week until week 12. Clinical relevance was defined as bleeds requiring intervention by healthcare professionals or causing pain or any other kind of harm. A prophylactic effect of emicizumab was assumed if the mean bleeding rate was significantly below 0.15 bleeds per patient-week, the rate observed in the GTH-AH 01/2010 study in patients receiving IST but no emicizumab. Secondary endpoints included thromboembolic events and mortality until week 24. **Results**: Forty-seven patients were enrolled (24 males, 23 females; median age 76 years [interquartile range 66-80], FVIII 1.4 IU/dl [0.3-5.6], inhibitor 11.4 BU/ml [3.9-43]). The primary efficacy criterion was met with an observed rate of 0.04 bleeds per patient-week ($p < 0.001$). 70% of patients had zero breakthrough bleeds. Two thromboembolic events were observed. Four deaths occurred (two related to bleeding, one infection, one cardiac arrest, none related to emicizumab). The overall survival rate was 91% after 24 weeks. **Conclusion(s)**: According to a predefined efficacy criterion, emicizumab was effective in preventing bleeds in AHA patients not treated with IST. The incidence of thromboembolic events was similar to historic registry studies and mortality from infections appeared low. These results suggest that patients with AHA can be managed with emicizumab prophylaxis.

Anti-emicizumab Antibodies do not Cross-react with Mim8 in vitro

https://doi.org/10.1016/j.rpth.2023.102161

In a research letter published in Research and Practice in Thrombosis and Haemostasis in July 2023, researchers from the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre in Milan evaluated the in vitro cross-reactivity of MIM8 with the anti-emicizumab antibodies in order to verify whether MIM8 could be a potential alternative therapeutic option for patients who can no longer be treated with emicizumab because of antidrug antibodies (ADAs). Analyses were performed in vitro on samples from 4 patients who had developed fully or partially neutralizing ADAs to emicizumab. Although the study is limited by the low number of patients, the authors found that the mim8 molecule could escape the anti-emicizumab antibodies. This suggests that patients who failed the treatment using emicizumab for ADA occurrence and need to resume the conventional therapies might benefit from mim8 maintaining a similar therapeutic approach without returning to intravenous infusion. Further investigation will clarify whether mim8 could be a good candidate for patients with HA who develop ADAs associated with low drug efficacy.

Bispecific Antibodies Mimicking Factor VIII in Haemophilia A: Converting Innovation to an Essential Medicine

https://doi.org/10.1016/j.rpth.2023.100173

In a *Forum* article published in Research and Practice in Thrombosis and Haemostasis in May 2023, Cedric Hermans and Glenn Pierce write that preventive subcutaneous treatment of severe haemophilia A with bispecific antibodies that mimic the action of coagulation factor VIII (FVIII) is emerging as an effective alternative to replacement therapy with intravenous administration of FVIII concentrates, either derived from plasma or produced by biotechnology. The therapeutic role of emicizumab has been studied and demonstrated in a large program of HAVEN clinical trials involving children and adults with haemophilia A, with and without inhibitors, treated weekly or less frequently, i.e., every 2 to 4 weeks. These studies demonstrated the hemostatic efficacy and safety of emicizumab, with low rates of breakthrough bleeding episodes. Access to this innovative therapeutic approach for a growing number of patients worldwide increasingly appears to be a priority public health strategy. Inclusion of FVIII mimetic bispecific antibodies on the World Health Organization essential medicines list would contribute to health equity in lower-income countries. In this context, emicizumab and other FVIII mimetic bispecific antibodies under development should become a part of the WHO Essential Medicines Program as a class for the treatment of severe haemophilia A. Priority should certainly be given to children and all patients with FVIII inhibitors to minimize joint damage and comorbidities, respectively.

Serious Bleeds in Pediatric Persons with Haemophilia A on Emicizumab Prophylaxis

https://doi.org/10.1016/j.rpth.2023.102238

In a *Brief Report* published in Research and Practice in Thrombosis and Haemostasis in September 2023, Garcia et al report real-world data on the effectiveness of **emicizumab** in children with haemophilia A. Clinical trials have shown success in bleed prevention with emicizumab, but real-world data on the effectiveness of emicizumab in preventing serious bleeds in the pediatric population are lacking. We completed a retrospective chart review of 37 pediatric male patients aged ≤18 years on emicizumab prophylaxis for a median duration of 30.5 months at Children's Medical Center in Dallas, Texas. Conclusion: This study highlights that serious bleeds, both provoked and unprovoked, can occur in pediatric persons with severe haemophilia A. These findings are important for clinicians to provide appropriate counseling/education and recommendation of treatment for pediatric persons with severe haemophilia A through shared decision making. Up-titration of emicizumab or factor VIII replacement needs consideration in persons with haemophilia with suboptimal bleeding control or who participate in activities categorized as moderate- to high-risk.

The von Willebrand factor-binding aptamer rondaptivon pegol as a treatment for severe and non-severe haemophilia A

https://pubmed.ncbi.nlm.nih.gov/36108308/

Introduction: In a paper published in Blood in March 2023, Ay et al assessed the safety, pharmacokinetics, and pharmacodynamics of **rondaptivon pegol (BT200)** in haemophilia A. Factor VIII circulates in a noncovalent complex with von Willebrand Factor (VWF), the latter determining FVIII half-life. The VWF-binding aptamer rondaptivon pegol (BT200) increases plasma levels of VWF/FVIII in healthy volunteers. **Methods**: Nineteen adult patients (ages 20-62 years, 4 women) with haemophilia A (8 mild, 2 moderate,

and 9 severe) received subcutaneous injections of rondaptivon pegol. After an initial fixed dose of 3 mg on days 0 and 4, patients received weekly doses of 2 to 9 mg until day 28. Severe haemophilia A patients underwent sparse-sampling population pharmacokinetics individual profiling after the final dose of rondaptivon pegol. Adverse events, pharmacokinetics, and pharmacodynamics were assessed. FVIII activity and VWF levels were measured. **Results**: All patients tolerated rondaptivon pegol well. The geometric mean half-life of rondaptivon pegol was 5.4 days and rondaptivon pegol significantly increased VWF levels. In severe haemophilia A, 6 doses of rondaptivon pegol increased the half-lives of 5 different FVIII products from a median of 10.4 hours to 31.1 hours (range, 20.8-56.0 hours). Median FVIII increased from 22% to 48% in mild haemophilia A and from 3% to 7.5% in moderate haemophilia A. **Conclusions**: Rondaptivon pegol is a first-in-class pro-hemostatic molecule that extended the half-life of substituted FVIII approximately 3-fold and increased endogenous FVIII levels approximately 2-fold in haemophilia patients. This trial was registered at www.clinicaltrials.gov as #NCT04677803.

Factor Replacement Therapies

Efanesoctocog Alfa Prophylaxis for Patients with Severe Haemophilia A

https://www.nejm.org/doi/full/10.1056/NEJMoa2209226

Introduction: In a paper published in NEJM in January 2023, von Drygalski et al report on a phase 3 study involving patients 12 years of age or older with severe haemophilia A. **Methods**: In group A, patients received once-weekly prophylaxis with **efanesoctocog alfa** (brand name **Altuviiio**) (50 IU per kilogram of body weight) for 52 weeks. In group B, patients received on-demand treatment with efanesoctocog alfa for 26 weeks, followed by once-weekly prophylaxis with efanesoctocog alfa for 26 weeks. The primary end point was the mean annualized bleeding rate in group A; the key secondary end point was an intra-patient comparison of the annualized bleeding rate during prophylaxis in group A with the rate during pre-study factor VIII prophylaxis. Additional end points included treatment of bleeding episodes, safety, pharmacokinetics, and changes in physical health, pain, and joint health. **Results:** In group A (133 patients), the median annualized bleeding rate was 0 (interquartile range, 0 to 1.04), and the estimated mean annualized bleeding rate was 0.71 (95% confidence interval [CI], 0.52 to 0.97). The mean annualized bleeding rate decreased from 2.96 (95% CI, 2.00 to 4.37) to 0.69 (95% CI, 0.43 to 1.11), a finding that showed superiority over pre-study factor VIII prophylaxis (P<0.001). A total of 26 patients were enrolled in group B. In the overall population, nearly all bleeding episodes (97%) resolved with one injection of efanesoctocog alfa. Weekly prophylaxis with efanesoctocog alfa provided mean factor VIII activity of more than 40 IU per deciliter for the majority of the week and of 15 IU per deciliter at day 7. Prophylaxis with efanesoctocog alfa for 52 weeks (group A) improved physical health (P<0.001), pain intensity (P=0.03), and joint health (P=0.01). In the overall study population, efanesoctocog alfa had an acceptable side-effect profile, and the development of inhibitors to factor VIII was not detected. **Conclusions:** In patients with severe haemophilia A, once-weekly efanesoctocog alfa provided superior bleeding prevention to pre-study prophylaxis, normal to near-normal factor VIII activity, and improvements in physical health, pain, and joint health. The study was funded by Sanofi and Sobi.

Efanesoctocog Alfa Prophylaxis for Previously Treated Patients <12 Years of Age with Severe Haemophilia A

https://doi.org/10.1016/j.rpth.2023.100288

Introduction: In a late-breakthrough oral presentation at ISTH and abstract published in Research and Practice in Thrombosis and Haemostasis in October 2023, Malec et al evaluated the safety, efficacy, and pharmacokinetics (PK) of **efanesoctocog alfa** (brand name **Altuviiio**) in PTP (< 12 years) with severe haemophilia A (XTENDKids, NCT04759131). Efanesoctocog alfa is a new class of high sustained factor VIII (FVIII) replacement therapy designed to overcome the von Willebrand factor-imposed half-life ceiling. In the pivotal XTEND-1 study, once-weekly efanesoctocog alfa 50 IU/kg provided normal to near-normal FVIII activity (>40 IU/dL) for most of the week and superior bleed protection versus pre-study prophylaxis in previously treated patients (PTP; ≥12 years) with severe haemophilia A. **Methods**: Patients received once-weekly efanesoctocog alfa 50 IU/kg for 52 weeks. The primary endpoint was the incidence of FVIII inhibitor development. Secondary endpoints included PK, annualized bleed rates (ABRs), efficacy for bleed treatment and perioperative management, and safety. Seventy-four male PTPs participated (< 6 years n = 38; 6– < 12 years n = 36). The mean (SD) efficacy period was 49.81 (6.61) weeks. **Results**: Inhibitors to FVIII were not detected (0% [95% confidence interval (CI)] 0–4.9]). The mean half-life was 40.2 hours, with mean FVIII activity >40 IU/dL for 3 days, >15 IU/dL for ∼5 days, and >10 IU/dL for ∼7 days at steady state. Median (interquartile range) and mean ABRs (95% CI) were 0.00 (0.00–1.02) and 0.89 (0.56–1.42), respectively. Most bleeds resolved with a single 50 IU/kg dose, and response to treatment was excellent/good for 98% of evaluated injections. Perioperative hemostasis was excellent in both major surgeries. Nine patients experienced ≥1 serious treatment emergent adverse event. No adverse events led to treatment discontinuation. **Conclusions**: Researchers concluded that once-weekly efanesoctocog alfa was well tolerated and provided highly effective bleed protection and treatment in children with severe haemophilia A. High sustained factor activity was within normal to near-normal levels (>40%) for 3 days and at ∼10% at Day 7. FVIII inhibitor development was not detected. The research was funded by Sanofi and Sobi.

Gene Therapy

Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Haemophilia A

https://www.nejm.org/doi/full/10.1056/NEJMoa2211075

Introduction: In a paper published in NEJM in February 2023, Mahlangu et al report on an open-label, single-group, multicenter, phase 3 trial in which 134 men with severe haemophilia A, who were receiving factor VIII prophylaxis, received a single infusion of 6×10^{13} vector genomes of **valoctocogene roxaparvovec** (brand name **Roctavian**) per kilogram of body weight. Valoctocogene roxaparvovec delivers a B-domain–deleted factor VIII coding sequence with an adeno-associated virus vector to prevent bleeding in persons with severe haemophilia A. **Methods:** The primary end point was the change from baseline in the annualized rate of treated bleeding events at week 104 after receipt of the infusion. The pharmacokinetics of valoctocogene roxaparvovec were modeled to estimate the bleeding risk relative to the activity of transgene-derived factor VIII. **Results:** At week 104, a total of 132 participants, including 112 with data that were prospectively collected at baseline, remained in the study. The mean annualized treated bleeding rate decreased by 84.5% from baseline (P<0.001) among the participants. From week 76 onward, the trajectory of the transgene-derived factor VIII activity showed first-order elimination kinetics; the model-estimated typical half-life of the transgene-derived factor VIII production system was 123 weeks (95% confidence interval, 84 to 232). The risk of joint bleeding was estimated among the trial participants; at a transgene-derived factor VIII level of 5 IU per deciliter measured with chromogenic assay, we expected that participants would have 1.0 episode of joint bleeding per year. At 2 years post-

infusion, no new safety signals had emerged and no new serious adverse events related to treatment had occurred. **Conclusions:** The study data show the durability of factor VIII activity and bleeding reduction and the safety profile of valoctocogene roxaparvovec at least 2 years after the gene transfer. Models of the risk of joint bleeding suggest that the relationship between transgene-derived factor VIII activity and bleeding episodes is similar to that reported with the use of epidemiologic data for persons with mild-to-moderate haemophilia A. The study was funded by BioMarin Pharmaceutical.

Four-Year Follow-up of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Haemophilia A (1054)

https://ash.confex.com/ash/2023/webprogram/Paper179422.html

Blood. 2023 Oct 23:blood.2022018971. doi: 10.1182/blood.2022018971.

Introduction: In an oral presentation and abstract at the ASH Annual Meeting in December 2023, Rupon et al present updated results with nearly 4 years of follow-up on an ongoing gene therapy study in participants with severe haemophilia A (FVIII activity <1%). The phase 1/2 Alta study (NCT03061201) is a dose-ranging study of **giroctocogene fitelparvovec** (PF-07055480, previously called SB-525), a recombinant AAV serotype 6 vector encoding a modified B-domain–deleted *F8* coding sequence. **Methods**: Four ascending doses of giroctocogene fitelparvovec (9e11, 2e12, 1e13, and 3e13 vg/kg) were infused into adults aged ≥18 years with severe haemophilia A across 4 cohorts (n=2 each). The high-dose (3e13 vg/kg) cohort was expanded to 5 participants. Key endpoints included safety, circulating FVIII activity, use of FVIII replacement therapy, and frequency of bleeding events. **Results:** Eleven male participants were enrolled in the study (mean [SD] age, 30.3 [7.8] years; White, 81.8%). As of the cutoff date (May 19, 2023), participants had been followed for 153 to 290 weeks. Two participants left the study after Week 156. Of the remaining, 1 participant had not yet completed 4 years (208 weeks). The most common treatment-related adverse events (AEs) reported in the high-dose cohort (n=5) were elevated liver enzymes and infusion-related reactions: increased alanine aminotransferase (ALT; n=3 [60.0%]), increased aspartate aminotransferase (AST; n=2 [40.0%]), pyrexia (n=3 [60.0%]), and tachycardia (n=2 [40.0%]). Treatment-related serious AEs were reported in 1 participant in the high-dose cohort who experienced hypotension and fever, with onset ≈6 h after infusion; the events fully resolved with treatment. AEs (all causality) of ALT increases requiring ≥7 days of corticosteroids were observed in 4 of 5 participants in the high-dose cohort. ALT elevations were managed with tapering courses of corticosteroids (median duration: 56 days; range: 7–135 days), with maintenance of efficacious levels of FVIII activity. Participants in the high-dose cohort have not required steroids since Week 65, have had ALT values in the normal range (follow-up: 156–208 weeks) and normal findings via liver MRI (follow-up: 104–208 weeks). No participant developed a confirmed inhibitor to FVIII. No thrombotic events or liver masses have been detected. Of the 5 participants in the high-dose cohort, 2 had data available through Week 208 and FVIII activity was maintained in the mild to normal range, consistent with Week 156 results. Of those without Week 208 data, 2 had data through Week 182. One participant maintained FVIII activity in the mild range (14.1% and 24.1% of normal, measured with a chromogenic and 1-stage assay, respectively); the other had FVIII activity of 3.1% and 7.2%. The remaining participant left the study after Week 156, with FVIII activity maintained in the mild range (11.8% and 22.9%). In the high-dose cohort, the mean annualized total bleeding rate [(number of all bleeding episodes starting 3 weeks after study drug infusion) / (observation period in years)] was 0 for the first year post infusion and 1.2 (SD 2.58) throughout the total duration of follow-up. In this cohort, the participant with the lowest FVIII activity level experienced a total of 22 bleeds, with 21 necessitating treatment (8 traumatic; 7 spontaneous; 6 unknown). The other 4 participants had no or very minimal bleeds, including 1 who experienced a bleed in a target joint. No

participants in the high-dose cohort have resumed prophylaxis. **Conclusion:** A single infusion of giroctocogene fitelparvovec gene therapy in participants with severe haemophilia A remains generally well tolerated over a period of nearly 4 years post infusion, with associated increases in FVIII levels in the moderate to normal range, without sustained AEs and with no AEs associated with increased liver function tests since Week 59. The ongoing phase 3 study (NCT04370054) in a larger cohort will provide more long-term data on the safety and durability of giroctocogene fitelparvovec in participants with moderately severe to severe haemophilia A.

GO-8: Stable Expression of Factor VIII over 5 Years Following Adeno-Associated Gene Transfer in Subjects with Haemophilia a Using a Novel Human Factor VIII Variant (3624)

https://ashpublications.org/blood/article/142/Supplement%201/3624/500955/GO-8-Stable-Expression-of-Factor-VIII-over-5-Years

Introduction: In an abstract at the ASH Annual Meeting in December 2023, Chowdary et al study liver-directed adeno-associated virus (AAV) gene therapy for haemophilia A (HA) that uses 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). In preclinical studies, AAV-HLP-hFVIII-V3 mediated a 3-fold higher FVIII expression when compared to an identical AAV construct encoding the hFVIII-SQ variant used in most HA gene therapy trials. **Methods**: In a multi-centre, open-label, non-randomised, 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 severe haemophilia A (FVIII activity ≤1%). All participants received prophylactic glucocorticoids, with or without tacrolimus, with the aim of reducing the risk of vector-related transaminase elevation. The primary endpoints were safety and efficacy. Efficacy was assessed by measuring FVIII activity (FVIII: C) using both chromogenic and one-stage clotting assays and factor consumption pre and post-gene therapy. **Results**: As of May 31, 2023, 12 participants were enrolled sequentially into one of four vector doses: 6×1011 vector genomes (vg)/kg body weight (n=1), 2×1012 vg/kg (n=3), 4×1012 vg/kg (n=3), or 6×1012 vg/kg (n=5). All participants were on FVIII prophylaxis prior to gene therapy. The most common vector-related adverse event was an elevation in live aminotransferase levels, which occurred in 10 of 12 participants. In 7 of the 8 participants treated at doses ≥4×1012 vg/kg, recurrent elevation in aminotransferase levels was observed during the first 12 months, often associated with tapering of immunosuppression. This resulted in a reduction in transgene expression from peak levels in all participants, with a complete loss of transgenic protein in one participant. Vector-related elevation in aminotransferase was not observed after the 12-month time point in long-term follow-up. Mean chromogenic FVIII: C levels at 12 months after gene therapy were 3 IU/dL in the 6×1011 vg/kg cohort, 13±9IU/dL (range: 2-19 IU/dl) in the 2×1012 vg/kg cohort, 8±1IU/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 then stably maintained over a median follow-up of 3 years (range: 0.2-5 years) from the level achieved 1-year post-infusion, best illustrated by the data from the 2×1012 and 4×1012 vg/kg cohorts. FVIII: C was, on average 2-fold higher when measured using a one-stage clotting assay compared to the chromogenic method. Nine of the 12 participants remained off prophylaxis after gene therapy for the duration of the follow-up period. Baseline mean and median annualised factor VIII use was 4097 and 4657 IU/kg per year before gene therapy. Following gene therapy, the mean and median annualised factor VIII concentrate use reduced across all participants to 1186 and 61 IU/kg (One sample t-test p=0.0009), respectively. No FVIII inhibitors or thrombotic events were reported for the duration of the study. **Conclusions**: 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 severe haemophilia A. A high rate of liver aminotransferase elevation following gene

transfer impacted transgene expression. However, 9 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.

Potential Haemophilia A Gene Therapy SPK-8011 Moves to Phase 3

https://haemophilianewstoday.com/news/haemophilia-a-gene-therapy-spk-8011-phase-3/

In an article published in Haemophilia News Today in July 2023, it is reported that Roche is moving into a Phase 3 clinical trial with its haemophilia A gene therapy **dirloctogene samoparvovec**, also know as SPK-8011. Data from the Phase 1/2 study and it showed the therapy increased FVIII activity in 21 of 23 patients. The two exceptions were patients who had experienced an immune reaction against the viral vector that the therapy uses to deliver its genetic payload. In the 21 patients who experienced an increase in FVIII activity, average annual bleeding rates decreased by more than 90% after up to five years of follow-up. At the same time, however, Roche announced it is discontinuing the development of another investigational haemophilia A gene therapy called SPK-8016, which was targeting patients with inhibitors to FVIII, stating that SPK-8016 "wasn't having the impact that we thought that it was going to have."

Assessment of Transduction of CD34+ Human Hematopoietic Stem Cells from Patients with Severe Haemophilia-A with Lentiviral Vector Carrying a High Expression FVIII Transgene (CD68-ET3-LV) (481)

https://ashpublications.org/blood/article/142/Supplement%201/481/504284/Assessment-of-Transduction-of-CD34-Human

Introduction: In an oral presentation at the ASH Annual Meeting in December 2023, Srivastava et al report here successful transduction of severe haemophilia A patient derived human hematopoietic stem cells with a lentiviral vector. Alternative strategies are needed for the large number of people with haemophilia who are ineligible for AAV based gene therapy due to age or high levels of anti-AAV neutralizing antibodies. High inter-individual variability of expression and ill sustained factor levels are also challenges with AAV based gene therapy for haemophilia A, in particular. The authors have developed a third-generation lentiviral vector mediated hematopoietic stem cell-based gene therapy for haemophilia A. (Doering et al Human Gene Therapy 2018; 29: 1183-1201) This vector (CD68-ET3-LV) has a high expression FVIII transgene with a CD68 promoter targeting expression in monocytic cells predominantly. **Methods:** Mobilized peripheral blood stem cells were collected by apheresis from three patients with severe haemophilia A without inhibitors who also received prophylactic clotting factor replacement therapy during this period. CD34+ hematopoietic stem cells (HSCs) were enriched on the CliniMACS Plus® system (Miltenyi Biotec, Bergish Gladbach, Germany) using the CliniMACS CD34® reagent system. Purified HSC were then transduced with this CD68-ET3-LV as follows - HSCs cultured on retronectin coated surfaces in xenofree media with cytokines were exposed to clinical grade CD68-ET3-LV vector in two ways – a double transduction protocol without any enhancer and a single transduction with an enhancer. After completion of this step, the product was assessed for viability and vector copy number (VCN) by trypan blue labelling and Q-PCR performed on genomic DNA from CFU cells, respectively. Transduced HSCs were also assessed for their engraftment potential. CD68-ET3-LV vector transduced HSC ($1x10^6$) were transplanted into NBSGW mice via tail vein injection. Engraftment was assessed at 16 weeks after transplantation. This protocol was approved by the Institutional Review Board of the Christian Medical College, Vellore, India. **Results:** G-CSF (10 ug/kg/day) based peripheral blood stem cell mobilization was well tolerated by all participants. The apheresis procedures which were done with plasma FVIII levels in the normal range after prophylactic replacement therapy were unremarkable. The total collection of mobilized CD34+ cells from the three donors was $268±80.5x10^6$ CD34+ cells. An aliquot of $2x10^6$ CD34+ cells/ml was used in the

transduction experiments. The data on viability and vector copy number post transduction shown in the tables 1 and 2 confirm that viability was not affected by the manipulation of these HSCs in both double and single transduction methods. The vector copy number (VCN) in the genomic DNA obtained from CFU cells collected from CD34+ HSCs cultured in MethoCult H4434™ (Stem Cell Technologies™, Vancouver, Canada) varied from 0.62 to 1.21 in double transduction (n=3) and nearly doubled in the single transduction method with an enhancer to VCNs of 1.5 and 2.4 in two samples tested. Transplantation studies in NBSGW mice showed successful engraftment of human CD34+ HSCs with a mean engraftment of 80.99 ± 4.2% of CD45+ multilineage hematopoietic cells in the bone marrow 16 weeks after transplantation. **Conclusion:** To the best of our knowledge, this is the first report of transduction of mobilized peripheral blood CD34+ HSCs from patients with severe haemophilia A using a clinical grade lentiviral vector with a high expression FVIII transgene. These data establish feasibility and safety of the procedure. The transduction protocol showed good efficiency with very high viability, significant VCN and good engraftment of these gene modified human HSCs in a mouse model. These protocols are currently being evaluated in a first in human phase 1 clinical trial of gene therapy for severe haemophilia A without inhibitors.

Factor Replacement Therapies

Factor IX Administration in the Skin Primes Inhibitor Formation and Sensitizes Haemophilia B Mice to Systemic Factor IX Administration

https://doi.org/10.1016/j.rpth.2023.102248

Introduction: In an original article published in Research and Practice in Thrombosis and Haemostasis in October 2023, Sherman et al aimed to develop a prophylactic immune tolerance protocol based on intradermal administration of FIX that would prevent inhibitor formation and/or anaphylaxis in response to replacement therapy. Factor IX inhibitor formation is the most serious complication of replacement therapy for the bleeding disorder haemophilia B, exacerbated by severe allergic reactions occurring in up to 60% of patients with inhibitors. Low success rates of immune tolerance induction therapy in haemophilia B necessitate the search for novel immune tolerance therapies. Skin-associated lymphoid tissues have been successfully targeted in allergen-specific immunotherapy. **Methods**: The investigators measured FIX inhibitor, anti-FIX immunoglobulin G1, and immunoglobulin E titers using the Bethesda assay and enzyme-linked immunosorbent assay after 4 weeks of twice-weekly intradermal FIX or FIX-Fc administration followed by 5 to 6 weeks of weekly systemic FIX injections in C3H/HeJ haemophilia B mice. They also measured skin antigen-presenting, follicular helper T, and germinal center B cell frequencies in skin-draining lymph nodes after a single or repeat intradermal FIX administration. **Results**: Intradermal administration enhanced FIX inhibitor formation in response to systemic administration. They further found that intradermal administration alone triggers inhibitor formation, even at a low dose of 0.4 IU/kg, which is 100-fold lower than the intravenous dose of 40 IU/kg typically required to induce inhibitor development in haemophilia B mice. Also, intradermal administration triggered germinal center formation in skin-draining lymph nodes and sensitized mice to systemic administration. Factor IX–Fc fusion protein did not modulate inhibitor formation. **Conclusion**: Intradermal FIX administration is highly immunogenic, suggesting that the skin compartment is not amenable to immune tolerance induction or therapeutic delivery of clotting factors. This work was supported by a Bayer Haemophilia Award and a National Institutes of Health, National Heart, Lung, and Blood Institute grant.

Gene Therapy

Stable Therapeutic Transgenic FIX Levels for More Than 10 Years in Subjects with Severe Haemophilia B Who Received scAAV2/8-LP1-Hfixco Adeno-Associated Virus Gene Therapy (1056)

https://ash.confex.com/ash/2023/webprogram/Paper186891.html

Introduction: In an oral presentation and abstract at the ASH Annual Meeting in December 2023, Reiss et al now report durable efficacy and long-term safety over at least 10 years of follow-up in 10 adults with severe haemophilia B (FIX activity ≤1%) who received the first-in-human, haemophilia B gene therapy. This was achieved following a single intravenous infusion of a self-complementary adeno-associated virus

(scAAV) vector containing the wild-type FIX gene (codon-optimized), under the control of a synthetic liver-specific promoter and pseudotyped AAV8 capsid (scAAV2/8-LP1-hFIXco; ClinicalTrials.gov:NCT00979238). **Results:** As of December 31, 2022, the median follow-up was 10.7 years (range 4-12 years). A total of 11 treatment-related adverse events occurred in 10 participants, including transient elevation of liver transaminases within 3 months of vector infusion in 4 of 6 patients treated with the high vector dose, without any recurrence. Two new serious adverse events were reported: (1) non-mucinous lung adenocarcinoma in situ, identified incidentally following a bullectomy for spontaneous pneumothorax 5 years after gene therapy in a 48-year-old participant considered not related to gene therapy following molecular studies, and (2) adenocarcinoma of the prostate in a 72-year-old participant 12 years after gene therapy. Tissue evaluation of the latter case is ongoing. No FIX inhibitors, thrombosis, persistent transaminitis or deaths were observed. Transgenic FIX expression has remained stable, with mean (±SD) FIX activity (one-stage) for the three dose cohorts of 1.7±0.9, 2.3±0.9 and 4.9±2.2 IU/dL, respectively. The mean and median ABR over the 10-year period following gene therapy of all 10 participants were 1.95 and 1.6 compared to 16.5 and 14, respectively, before gene therapy. This represents an 8.5-fold reduction in bleeding events (Wilcoxon signed rank test p=0.002). In the 6 high-dose participants, the ABR was 21-fold lower (mean=1.16, median 1, paired t-test, p<0.008). Mean and median FIX concentrate usage before gene therapy in the 10 participants were 2869 and 2526 IU/kg dropping to 945 and 274 IU/kg, respectively, over a 10-year period after gene therapy (p=0.0003). All participants developed a persistent, high-titer polyclonal anti-AAV8 capsid-specific antibody response after administration of scAAV2/8-LP1-hFIXco. **Conclusion:** Expression of transgenic FIX has remained stable over a period of 10 years following systemic administration of scAAV2/8-LP1-hFIXco resulting in sustained clinical benefit, with substantial reduction in ABR and FIX concentrate use.

Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Haemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Haemophilia B (1055)

https://ashpublications.org/blood/article/142/Supplement%201/1055/504219/Long-Term-Bleeding-Protection-Sustained-FIX

Introduction: In an oral presentation at the ASH Annual Meeting in December 2023, Pipe et al report long-term efficacy and safety data of **etranacogene dezaparvovec** (formerly AMT-061, brand name **Hemgenix**) from the HOPE-B trial over a period of 3 years post-treatment. Etranacogene dezaparvovec is the first approved gene therapy for haemophilia B in the US and Europe. It is an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene under the control of the liver-specific promoter LP-1. The pivotal phase 3 HOPE-B clinical trial (NCT03569891) of etranacogene dezaparvovec demonstrated superiority of bleeding protection compared to standard of care FIX prophylaxis up to 24 months post-treatment; long-term follow-up from Year 2 post-administration onward is currently ongoing. **Methods***:* In this pivotal phase 3 open-label, single-arm trial, adult male participants with severe or moderately severe haemophilia B (FIX ≤2%), with or without pre-existing AAV5 neutralizing antibodies (NAbs), were infused with a single dose (2×10^{13} gc/kg) of etranacogene dezaparvovec, following a ≥6-month lead-in period of receiving their usual FIX prophylaxis. Efficacy (bleeding rates, aPTT-based FIX activity levels, FIX consumption) and safety data (adverse events [AEs]) during Years 1, 2, and 3 post treatment with etranacogene dezaparvovec are reported. **Results***:* Of 54 participants who received etranacogene dezaparvovec, 52 completed 36 months of follow-up. Mean annualized bleeding rate (ABR) for all bleeds during Months 7-36 post-treatment was significantly reduced by 64% (mean ABR 1.52) compared with the ≥6-month lead-in period (mean ABR 4.17; *P*=0.0004). Total

number of bleeds (all types) were 136 during the ≥6-month lead-in period and decreased to 55 during Year 1, 48 during Year 2, and 37 during Year 3 post-treatment. Median [range] bleeds per participant decreased from 2.0 [0-10] during the lead-in period and remained stable to 0.0 [0-4] during Year 1, 0.0 [0-10] during Year 2, and 0.0 [0-8] during Year 3. Superior bleeding protection was in line with the level of transgene-derived endogenous FIX expression. The mean±SD (median; range) endogenous FIX activity level (ie. in the absence of exogenous FIX exposure) of participants was 41.5 IU/dL ±21.7 (39.9; 5.9-113, n=50) at Year 1, 36.7 IU/dL ±19.0 (33.9; 4.7-99.2, n=50) at Year 2, and sustained at 38.6 IU/dL ±17.8 (36.0; 4.8-80.3, n=48) at Year 3 post-treatment. Pharmacodynamic profile was not significantly different in participants with AA5 NAb undetected or titer ≤1:678. At 3 years post-treatment, 51 (94%) remained free of continuous FIX prophylaxis. One participant who lacked efficacy (highest AAV5 NAbs titer of 1:3212) and 1 who received a 10% partial dose of treatment did not discontinue prophylaxis; 1 participant eventually had his FIX levels declined to 2-5% range; his bleeding phenotype returned, and he resumed prophylaxis per protocol at month 30 post-treatment. During Year 2 and Year 3 post-treatment, 37 (70%) and 39 (75%) participants received no FIX infusion, respectively. Overall mean annualized FIX consumption decreased by 96% over 3 years post-treatment compared to the ≥6-month lead-in period (–246,763 IU/kg/participant, including those receiving FIX prophylaxis post-treatment; *P*<0.0001). During the 3 years post-dose, all participants experienced at least 1 treatment-emergent AE (TEAE); of 709 events, 541 (76%) were mild, 137 (19%) were moderate, and 31 (4%) were severe. There were no serious AEs related to treatment [a serious AE of hepatocellular carcinoma (HCC) and a death were reported previously before Year 2 and determined to be unrelated to treatment]. A total of 38/54 (70%) participants experienced 96 treatment related TEAEs, of which 95% occurred before 6 months post-treatment. The most common AE was an increase in alanine transaminase (ALT), for which 9 (16.7%) participants received supportive care with reactive corticosteroids for a mean duration of 81.4 days (SD: 28.6; range: 51-130 days). No new deaths, no new HCC, and no late treatment-related ALT elevations or thromboembolic events were reported. **Conclusion***:* Long-term follow-up during the HOPE-B trial has shown that a single-dose of etranacogene dezaparvovec resulted in long-term endogenous FIX Padua expression and superior bleeding protection compared to FIX prophylaxis in participants without or with AAV NAb titer ≤1:678, with a favorable safety profile over 3 years post-administration.

Adult Patients with Haemophilia B and with a History of Chronic HCV/HBV Infection Receiving Liver-Directed Gene Therapy Demonstrated Long-Term Bleeding Protection and Sustained FIX Activity: Efficacy and Safety Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene (2258)

https://ashpublications.org/blood/article/142/Supplement%201/2258/500355/Adult-Patients-with-Haemophilia-B-and-with-a

Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, von Dryglaski et al evaluate the efficacy and safety of **etranacogene dezaparvovec** in the subset of HOPE-B participants with a history of chronic HCV and/or HBV. Liver-targeted recombinant adeno-associated virus (rAAV) gene therapy for haemophilia B has recently become a real-world therapeutic option for an adult population burdened with prevalent co-morbid chronic hepatitis C virus (HCV) and hepatitis B virus (HBV). The pivotal phase 3 HOPE-B trial (NCT03489291) evaluated the efficacy and safety of etranacogene dezaparvovec (CSL222, formerly AMT-061), an AAV5 vector, containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene under the control of the liver-specific promoter LP-1. **Methods**: Adult male participants with haemophilia B (FIX ≤2%), were infused with a single dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg), following a ≥6-month lead-in period receiving their usual FIX prophylaxis. Relevant exclusion criteria included baseline liver chemistries > 2X the upper limit of normal (ULN); active HCV (HCV

RNA detectable), HBV (HBV DNA detectable or HBV sAg reactive) or uncontrolled HIV infection; or advanced liver fibrosis (FibroScan™ score of ≥9 kPa). Regular liver ultrasound screening, serum chemistries, and alphafetoprotein (AFP) were collected along with FIX expression and bleeding data. During the first months post-treatment, alanine aminotransferase (ALT) increase to 2X the subject's baseline or >ULN was treated with a per-protocol tapering course of oral corticosteroids. **Results**: Among 54 HOPE-B trial participants, 31 (57.4%) had history of co-morbid chronic HCV, without active disease and with undetectable HCV RNA. Of these 31 subjects, 7 had a history of chronic HBV infection without active disease (HBV DNA undetectable; HBV sAg neg). Two subjects were HCV/HIV co-infected (HIV DNA neg; CD4+ T-cell count >200). Two subjects were HBV+ (HBV env AB reactive, HBV sAg non-reactive, HBV DNA undetectable)/HCV-/HIV-. The mean age in the HCV+ and/or HBV+ subgroup (HCBV n=33) was 50.0 years (range 31-75). All HCBV participants had central lab (CL) ALT <ULN (ULN=41 U/L) on the day of dosing except one subject who had a CL ALT of 48 U/L. The mean screening fibroscan (liver elastography) score for this subgroup was 5.2 kPa (range 2.8-8.0). In HCBV participants 16/33 (48.5%) had pre-existing AAV5 neutralizing antibodies (NAb), with titers ranging from 8.5-3232; all NAb+ HCBV patients had titer ≤678 except one participant who had a titer of 3212 and never demonstrated FIX expression; as a result his prophylactic FIX infusions were never discontinued and his efficacy outcomes reflect exogenous FIX therapy. One HCBV participant returned to continuous routine prophylaxis 30 months post treatment. In the HOPE-B trial 11/54 (20.4%) of participants had 12 adverse events of ALT elevation of 2X above baseline or >ULN within 12 weeks after etranacogene dezaparvovec treatment, which triggered immunosuppressive therapy with corticosteroids in 9/54 (16.7%) participants. In the HCBV subgroup, 5/33 (15.2%) participants had ALT elevations of which 4/33 (12.1%) participants received corticosteroids. As reported previously (Schmidt M, et al. Blood Advances. 2023), one HCBV subject maintained normal AFP levels however per-protocol screening ultrasound at one year after gene therapy this participant developed a hepatocellular carcinoma (HCC); molecular characterization demonstrated the HCC was not related to etranacogene dezaparvovec treatment. Factor IX expression was stably increased above baseline throughout 36 months after the single CSL222 infusion. History of chronic HCBV did not impact FIX expression. After excluding the subject with the pre-existing AAV5 NAb titer 3212 whose continued prophylaxis use confounds analysis, the mean annualized bleeding rate (ABR) decreased after gene therapy compared to lead-in standard of care FIX prophylaxis. HCBV participants demonstrated an ABR rate ratio of 0.31 (95% CI 0.13, 0.72) indicating 69% reduction in all bleeding, sustained from months 7-36 following etranacogene dezaparvovec treatment. **Conclusions**: The majority of HOPE-B trial participants were adults with a history of chronic HCV and/or HBV infection without active viral disease or evident pre-existing liver fibrosis. Safety and efficacy are observed in the HCBV participants.

Efficacy and Safety of Fidanacogene Elaparvovec in Adults with Moderately Severe or Severe Haemophilia B: Results from the Phase 3 BENEGENE-2 Gene Therapy Trial

https://doi.org/10.1016/j.rpth.2023.100452

Introduction: In an abstract presented at ISTH and published in Research and Practice in Thrombosis and Haemostasis in October 2023, Cuker et al evaluate the efficacy and safety of **fidanacogene elaparvovec** (brand name **Beqvez**) in participants with moderately severe or severe haemophilia B. Fidanacogene elaparvovec (PF-06838435, formerly SPK-9001) is an adeno-associated virus-based gene therapy vector transferring the high-activity variant of human factor IX (FIX) FIX-R338L for the treatment of haemophilia B. **Methods**: BENEGENE-2 (NCT03861273) is a phase 3, open-label, single-arm trial that enrolled adult males with haemophilia B (FIX:C ≤2 IU/dL) who had 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. Other secondary endpoints included annualized FIX consumption, ABR of specific bleed types (eg,spontaneous), and frequency of target joint bleeds. Adverse events (AEs) were monitored. Participants provided written informed consent and the study was approved by the relevant regulatory/ethics committees. **Results**: Forty-five participants (median [range] age, 29 [18, 62] years) were dosed with fidanacogene elaparvovec. Total ABR was reduced by 71% post-fidanacogene elaparvovec treatment vs prophylaxis (mean ABR, 1.3 vs 4.4; P < 0.0001; Table 1) and was stable over time (0.4 at Year 3; n = 21). Mean FIX activity, measured by one-stage SynthASil, one-stage Actin-FSL, and chromogenic assays, was 27.5% at Month 15. FIX activity remained relatively stable at Month 24. Twenty-eight participants (62%) received corticosteroids for presumed immune response. No deaths, infusion-related serious AEs, 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.

Characterizing a Cohort of Patients with Haemophilia B Treated with Fidanacogene Elaparvovec from the Phase 3 Benegene-2 Study Who Returned to Factor IX Prophylaxis (2257)

https://ashpublications.org/blood/article/142/Supplement%201/2257/502711/Characterizing-a-Cohort-of-Patients-with

Blood (2023) 142 (Supplement 1): 2257. https://doi.org/10.1182/blood-2023-181223

Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, Frenzel et al describe the characteristics of the return-to-prophylaxis (RTP) participants. **Fidanacogene elaparvovec** (brand name **Beqvez**, PF-06838435, formerly **SPK-9001**) is an adeno-associated virus (AAV)–based gene therapy designed to deliver a high-activity human factor IX (FIX) variant transgene, FIX-R338L, resulting in endogenous FIX production in people with haemophilia B. To date, 45 participants with moderately severe to severe (FIX:C ≤2%) haemophilia B have received fidanacogene elaparvovec as part of the ongoing phase 3 study, BENEGENE-2 (NCT03861273). Of these 45 participants, 6 returned to prophylaxis of FIX after initially responding to treatment. **Methods:** Participants with baseline FIX activity ≤2% received a single dose of 5e11 vg/kg fidanacogene elaparvovec (AAVrh74 variant) as part of the phase 3 study (N=45). Participants suspended prophylaxis following vector infusion (1 participant continued for 2 weeks post infusion), which could be resumed per the investigator's discretion and the protocol provided guidance for when to consider resuming prophylaxis: ≥2 consecutive central laboratory FIX activity levels ≤2% at least 2 weeks apart and/or ≥2 spontaneous joints bleeds within 4 weeks and/or ≥3 spontaneous bleeds overall (joint and non-joint). **Results:** Prior to fidanacogene elaparvovec infusion, all 45 participants had completed at least 6 months of prophylaxis as part of the lead-in study (BENEGENE-1, NCT03587116). The mean age (range) of all 45 study participants was 33.2 y (18–62) and the 6 RTP participants had a mean age (range) of 28.3 y (18-47), of whom 4 were <30 y old. The region, race, and weight of the 6 RTP participants were representative of the entire study population (Table 1). All RTP participants initially responded to gene therapy and achieved peak FIX activity levels >5%, determined by one-stage actin-FSL (7–22.1%) and one-stage Synthasil (18.3–45.5%) across Days 36–97. Time to RTP from fidanacogene elaparvovec dose ranged from Days 155 to 623. The reasons reported for RTP were low FIX activity in 5 participants, of whom 1 had a prior history of intracerebral hemorrhage, and increased bleeds in 1 participant. Five participants recorded ≥1 bleeding event prior to resumption of prophylaxis. All RTP participants were treated with ≥1 course of corticosteroids for presumed cellular immune response. In all cases, maximum alanine aminotransferase was 1-2x upper limit of normal. Two RTP participants had an ELISPOT drawn within ±1 day of starting corticosteroids; both were negative for capsid peptides (Table 2).

In comparison, 4 participants who took corticosteroids but did not resume prophylaxis were positive for capsid. All 6 RTP participants had a decline in FIX activity from peak levels in the absence of inhibitors, but displayed variable decline prior to and during corticosteroid treatment, or after completion of corticosteroid wean, with and without some elevation of liver enzyme at the time of the decline. **Conclusion:** The 6 RTP participants who received fidanacogene elaparvovec in the phase 3 study (BENEGENE-2) initially responded to therapy before a heterogenous decline in FIX activity. The limited number of participants and lack of consistent patterns and demographic features make identifying predictors of potential RTP challenging. Although all RTP participants were treated with corticosteroids during this study, not all participants treated with corticosteroids RTP of FIX. Predictors of loss of response have not been identified and further work is ongoing to potentially identify factors associated with increased risk of RTP.

Bypassing Agents

Eptacog Beta (Cevenfacta) Efficacy and Safety in Underweight, Normal Weight, and Overweight/Obese Persons with Haemophilia A or B and Inhibitors

https://doi.org/10.1016/j.rpth.2023.100219

Introduction: In an abstract published in Research and Practice in Thrombosis and Haemostasis in August 2023, Srivastava et al evaluate **eptacog beta** (brand name **Cevenfacta**) efficacy and safety when treating mild or moderate bleeding episodes (BEs) with 75 and 225 µg/kg IDRs in underweight (body mass index [BMI] <18.5 kg/m2), normal weight (BMI 18.5-24.9 kg/m2), and overweight (BMI 25.0-29.9 kg/m2) or obese (BMI ≥30.0 kg/m2) PwHABI from PERSEPT 1, at 12 and 24 hours post-initial dose of eptacog beta. Being overweight or obese increases the disease burden faced by persons with haemophilia, and the prevalence of these comorbidities in persons with haemophilia may be rising along with that of the general population. Eptacog beta is a recombinant activated human factor VII proven to be safe and effective for the treatment and control of BEs in persons with haemophilia A or B with inhibitors (PwHABI) ≥12 years of age. **Methods**: The pivotal phase 3 trial (PERSEPT 1; NCT02020369) included 27 subjects ages ≥12 years who treated 465 mild or moderate BEs. Methods: PERSEPT 1 was a prospective, global, open-label trial using 75 and 225 µg/kg IDRs in a randomized crossover design. Subjects initially treated mild or moderate BEs with 75 or 225 µg/kg eptacog beta, followed either 3 hours (75 µg/kg IDR) or 9 hours later (225 µg/ kg IDR) with 75 µg/kg q3h as needed. Treatment success was defined as obtaining a hemostasis evaluation of “excellent” or “good” with no use of additional eptacog beta, alternative hemostatic agents or blood products, and no increase in pain following the first “excellent” or “good” assessment. **Results**: Eight PERSEPT 1 subjects were underweight and treated 193 BEs; 12 were of normal weight and treated 198 BEs; and 7 were overweight or obese and treated 74 BEs. At 12 hours, the 225 µg/kg IDR showed increased treatment success proportions over the 75 µg/kg IDR ($p<0.01$) for both normal weight and overweight/obese groups. At 24 hours post-initial eptacog beta infusion, nearly all BEs in each BMI group were successfully treated (89-98% for the 75 µg/kg IDR and 98-100% for the 225 µg/kg IDR). Six treatment-related adverse events (TRAEs; 4 infusion site discomfort and 2 infusion site hematoma events) were experienced in the normal weight group and 1 TRAE (increased body temperature) was experienced in the underweight group; all TRAEs resolved and were considered mild in nature. No thromboembolic, allergic, hypersensitivity, or anaphylactic events occurred, and no neutralizing antieptacog beta antibodies were detected in any BMI group. **Conclusions**: Increased efficacy was achieved at 12 hours with the 225 µg/kg IDR over the 75 µg/kg IDR in the normal weight and overweight/obese groups. Eptacog beta was

well tolerated in subjects across all BMI groups; no thromboembolic events were experienced by any subjects, including those in the overweight/obese group. With the high efficacy seen at 24 hours, eptacog beta offers an important treatment option for PwHABI of all BMI classes.

Rebalancing Agents

Subcutaneous Concizumab Prophylaxis in Patients with Haemophilia A or B with Inhibitors: Efficacy, Safety, and Physical Activity Score, Primary Analysis from the Phase 3 Explorer7 Trial

https://doi.org/10.1016/j.rpth.2023.100218

Introduction: In an abstract published in Research and Practice in Thrombosis and Haemostasis in August 2023, Wheeler et al assessed the safety and efficacy of **concizumab** (brand name **Alhemo**) PPX and compared physical activity and health economics in patients with HA and HB with inhibitors (HAwI, HBwI) on PPX vs no PPX. Concizumab, a recombinant monoclonal antibody used for inhibition of tissue factor pathway inhibitor, is a daily subcutaneous prophylaxis (PPX) treatment for patients with haemophilia A or B with inhibitors (HAwI or HBwI). **Methods:** In explorer7, patients were randomized 1:2 to no PPX (arm 1; n=19) or concizumab PPX (arm 2; n=33) or assigned to nonrandomized concizumab PPX (arms 3-4; n=82). During a program restart after a pause due to nonfatal thromboembolic events, patients on PPX received a 1.0 mg/kg loading dose, followed by a daily 0.20 mg/kg dose starting on day 2. The main part was completed after ≥24 weeks for arm 1 or ≥32 weeks for arms 2-4 and all patients received concizumab PPX in the extension. Adverse events were recorded by the investigator or patient. Using a negative binomial regression model, annualized bleed rate (ABR) was determined with haemophilia subtype, prescreening treatment mode, and bleeding frequency as factors. Physical activity data were collected through patient use of a tracker from baseline to the end of the main part. Baseline was defined as measurements from explorer6 when applicable, or collected between visit 1 and 2 prior to or following the treatment pause. An analysis of covariance was used to find the change in physical activity. Data on health economics were collected via patient completion of a monthly eDiary. **Results:** The percentage of patients with 0 treated bleeds during the first 24 weeks of treatment was 5.3% for no PPX vs 40.4% for concizumab PPX. The estimated mean ABR (95% CI) for treated spontaneous and traumatic bleeding episodes was 11.8 (7.03-19.86) for no PPX vs 1.7 (1.01-2.87) for PPX (ABR ratio, 0.14 (0.07-0.29)). After all patients switched to concizumab PPX, the overall median ABR was 0.0. No thromboembolic events were reported for concizumab treatment after the restart. Arm 2 demonstrated an increased percentage time spent in physical activity relative to awake time compared to arm 1 (difference estimate (95% CI); 4.41 (0.38-8.44) for moderate-to-vigorous and 4.18 (0.15-8.24) for moderate activity). **Conclusions**: The authors concluded that daily treatment of HAwI/HBwI with concizumab PPX effectively reduced bleeding episodes compared with no PPX, and concizumab was considered safe and well tolerated. An increased percentage of awake time was spent in moderate and moderate-to-vigorous physical activity, and there was no significant difference in health economic parameters in patients on concizumab PPX vs no PPX.

Efficacy and Safety of Concizumab Prophylaxis in Patients with Haemophilia A or B without Inhibitors: 56-Week Cut-Off Results of the Phase 3 explorer8 Study (2609)

https://ashpublications.org/blood/article/142/Supplement%201/2609/500352/Efficacy-and-Safety-of-Concizumab-Prophylaxis-in

Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, Astermark et al assess the longer-term efficacy and safety of daily **concizumab** (brand name **Alhemo**) prophylaxis in patients with HA/HB. Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development as a once-daily subcutaneous prophylactic treatment for haemophilia of all subtypes. Results from the 56-week cut-off of the prospective, multicenter, open-label explorer8 study (NCT04082429; phase 3) in patients with haemophilia A or B without inhibitors (HA/HB) are presented, further to the 32-week confirmatory analysis cut-off (CACO) results previously reported (Chowdary P et al. ISTH 2023, OC 59.1). **Methods**: Male patients (aged ≥12 years) with HA/HB were randomized 1:2 to no prophylaxis (arm 1; 24 weeks) or concizumab prophylaxis (arm 2; ≥32 weeks) or assigned to non-randomized concizumab prophylaxis (arms 3 and 4; ≥32 weeks). After the main part of the trial (24 weeks for arm 1), patients in arm 1 could switch to concizumab prophylaxis. After treatment restart following the treatment pause due to thromboembolic events, patients received a 1.0 mg/kg concizumab loading dose on Day 1, followed by an initial 0.20 mg/kg daily dose starting on Day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 4. Assessments at the 56-week cut-off included efficacy, safety, pharmacokinetic and pharmacodynamic measurements. Informed consent/ethics committee approval were obtained. **Results**: The study included 148 patients (HA, n=82; HB, n=66), of which 21 patients were randomized to no prophylaxis (arm 1: HA, n=9; HB, n=12), 42 patients to concizumab prophylaxis (arm 2: HA, n=18; HB, n=24) and the remaining 85 patients were assigned to concizumab prophylaxis (non-randomized arms 3 and 4). After the main part of the trial, 17 patients from arm 1 switched to concizumab prophylaxis, receiving the same dosing regimen as patients in arms 2–4 when first starting on concizumab. A total of 132 patients (HA, n=73; HB, n=59) completed the 56-week cut-off. The overall median (interquartile range) annualized bleeding rate (ABR) on concizumab prophylaxis in arms 1–4 was 1.7 (0.0–4.5) for HA and 2.8 (0.0–6.4) for HB (Table 1); these results were also supported by the supportive secondary efficacy assessments. After treatment restart, no thromboembolic events were reported (Table 2). A total of 30 serious adverse events (AEs) were reported in 20 patients at the 56-week cut-off. As previously reported at CACO, one patient experienced a serious AE with fatal outcome (intra-abdominal hemorrhage) and 6 patients experienced AEs leading to withdrawal of concizumab treatment. The rate of injection site reactions was comparable to CACO. No hypersensitivity type reactions were reported in the study and low-titer anti-concizumab antibodies were detected in a total of 21 patients at the 56-week cut-off, with no apparent impact on bleeds or AEs. Concizumab plasma concentration remained stable over time. Free TFPI and thrombin peak levels continued to be stable over time. **Conclusions:** Concizumab prophylaxis showed longer-term (≥1 year) efficacy in adult and adolescent patients with HA/HB at the 56-week cut-off, which was consistent with the results observed at CACO. Concizumab prophylaxis was considered safe and well tolerated in patients with HA/HB.

Surgical Procedures and Hemostatic Outcome in Patients with Haemophilia Receiving Concizumab Prophylaxis during the Phase 3 explorer7 and explorer8 Trials (30)

https://ashpublications.org/blood/article/142/Supplement%201/30/502616/Surgical-Procedures-and-Hemostatic-Outcome-in

Introduction: In an oral presentation at the ASH Annual Meeting in December 2023, Chan et al provide an overview of surgical procedures at the 56-week cut-off performed on patients who received **concizumab** (brand name **Alhemo**) prophylaxis in the explorer7 and explorer8 trials. Concizumab is an anti-tissue factor pathway inhibitor monoclonal antibody that has been developed for once-daily subcutaneous prophylactic treatment for haemophilia of all subtypes. The phase 3 explorer7 (NCT04083781) and explorer8 trials (NCT04082429) investigated the efficacy and safety of concizumab prophylaxis in patients

with haemophilia A or B with (HAwI/HBwI, explorer7) or without (HA/HB, explorer8) inhibitors. **Methods:** Patients in both explorer7 and explorer8 trials were exposed to no prophylaxis (arm 1) or concizumab prophylaxis (arms 2–4) based on their treatment regimen before the trial. After the main part of the trial, all patients (arms 1–4) could continue in the extension part of the trial receiving concizumab for up to 136 weeks. Informed consent/ethics committee approvals were obtained as appropriate. Minor surgical procedures (defined as any invasive operative procedure where only the skin, mucous membranes or superficial connective tissue is manipulated) were permitted during the explorer7 and explorer8 trials, and management of minor surgeries was at the investigator's discretion. Planned major surgery was not permitted, and for any cases of acute major surgery, a concizumab pause was recommended. Data regarding both minor and major surgeries undertaken in patients were collected at the 56-week cut-off of the trials. Local/topical use of anti-fibrinolytics was permitted during surgical procedures in both trials (single systemic doses allowed following benefit-risk evaluation) and patients undergoing minor surgical procedures continued to receive concizumab prophylaxis during the perioperative period (with no change to the dosage they received). **Results:** During both trials, a total of 278 patients received concizumab prophylaxis. Of these, 30 patients underwent a minor surgical procedure, including 6 (20.0%) adolescents (aged 12–17 years) and 24 (80.0%) adults (aged 18–64 years). Nine patients who underwent a minor procedure had HA (30.0%), 10 had HB (33.3%), 7 had HAwI (23.3%) and 4 had HBwI (13.3%). Four patients underwent both major and minor surgeries and 2 patients underwent major surgeries only. In total, 44 surgical procedures were undergone in 32 patients. The surgical procedures that were performed in patients who received concizumab included a range of minor surgeries in both trials (including tooth extractions and other dental procedures, port removal, colonoscopy, arthrodesis and urethral augmentation). Overall, 6 cases of major surgery were reported during the explorer7 and explorer8 trials (left hip arthropathy, hematoma drainage, right femoral neck fracture, total knee arthroplasty, right ankle arthropathy and diagnostic laparoscopy with removal of blood from the abdominal cavity) in 1 patient with HA, 2 patients with HB, 1 patient with HAwI and 2 patients with HBwI respectively. Bleeding episodes related to minor and major surgical procedures (n=30) were reported in 24 patients and in 15 of these a total of 17 bleeding episodes were treated. The majority of patients (n=12) who reported a treated surgical-related bleeding episode had undergone a dental surgical procedure. Other minor surgical procedures with associated bleeding episodes included port removal, and venesection. **Conclusions:** Minor surgical procedures were conducted in approximately 11% of patients who received treatment with concizumab during the phase 3 explorer7 and explorer8 trials. Most minor surgeries that took place were dental procedures and the majority of surgical-related bleeding episodes were mild or moderate. Overall, minor surgeries could be performed on patients with haemophilia under concizumab prophylaxis.

The Effect of Concizumab Prophylaxis on Target Joints, Resolution and Joint Bleeds in Patients With Haemophilia A or B With or Without Inhibitors in Phase 3 Clinical Trials (284)

https://ashpublications.org/blood/article/142/Supplement%201/284/502473/The-Effect-of-Concizumab-Prophylaxis-on-Target

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Introduction: In an oral presentation at the ASH Annual Meeting in December 2023, young et al assess and communicate the effect of longer term (56 weeks) **concizumab** (brand name **Alhemo**) prophylaxis (PPX) on target joints, their resolution, and joint bleeds in patients with haemophilia A or B with or without inhibitors. Concizumab is a recombinant anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody under development as a once-daily subcutaneous prophylactic treatment for haemophilia patients with and without inhibitors, and has the potential to be one of the first subcutaneous treatment options for

haemophilia B. Recurring joint bleeds may cause hemophilic arthropathy and reduce the quality of life of patients with haemophilia (van Vulpen LFD et al. *Haemophilia*. 2018; 24 Suppl 6:44-49). Results on target joints, their resolution, and joint bleeds in patients with haemophilia (haemophilia A or B with inhibitors [HAwI or HBwI] or without inhibitors [HA or HB]) from the prospective, multicenter, open-label explorer7 (NCT04083781) and explorer8 (NCT04082429) phase 3 concizumab clinical trials at the 56-week cut-off are presented. **Methods:** After informed consent/ethics committee approval were obtained, patients in both explorer7 and explorer8 trials were exposed to no PPX (arm 1) or concizumab PPX (arms 2–4) based on their treatment regimen before the trial. After the main part of the trial, all patients (arms 1–4) could continue in the extension part of the trial receiving concizumab for up to 136 weeks. Upon treatment restart following a treatment pause due to thromboembolic events, patients received a 1.0 mg/kg concizumab loading dose on Day 1, followed by an initial 0.20 mg/kg daily dose starting on Day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 4. The data presented here are from the 56-week cut-off that was defined as when all patients had completed the visit after 56 weeks or permanently discontinued treatment. Annualized bleeding rate (ABR) of joint bleeds was evaluated for all patients. Target joints at baseline by age group and target joint resolutions during the trial were assessed separately for this abstract. Target joints were defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-month period, and target joints were deemed resolved when there have been ≤2 bleeding episodes in the joint during the previous 12 months of exposure (Blanchette VS et al. *J Thromb Haemost.* 2014;12(11):1935–1939). **Results:** A total of 144 patients with HA or HB and a total of 127 patients with HAwI or HBwI were exposed to concizumab PPX at the 56-week cut-off. Upon treatment restart, 144 patients with HA or HB and 112 patients with HAwI or HBwI were included in the studies and were allocated to the new concizumab PPX dosing regimen, of which the majority were adults (HA + HB: 105; HAwI + HBwI: 72), some were adolescents (12–17 years) (HA + HB: 36; HAwI + HBwI: 40), and a few were elderly/very elderly (65–84 years) (HA + HB: 3; HAwI + HBwI: 0). Patients who had at least one target joint at baseline (HA + HB: adults [45/108], adolescents [18/36]; HAwI + HBwI: adults [35/72], adolescents [20/40]) mostly reported target joints in the ankle, elbow, and knee, and a few in the hip and shoulder. Of these patients who were exposed to concizumab PPX for at least 12 months, 49 patients with HA or HB reported a total of 80 target joints at baseline, of which 69 (86.3%) were resolved at the 56-week cut-off, and 49 patients with HAwI or HBwI reported 85 target joints at baseline, of which 78 (91.8%) were resolved at the 56-week cut-off. Most target joints were resolved within 12 months after treatment start (median [25th; 75th percentile])(12.0 months [12.0; 12.0]), both for patients with HA or HB and HAwI or HBwI. The median ABRs for treated spontaneous and traumatic target joint bleeding episodes were 0.0 for patients with HA or HB and HAwI or HBwI, and the median ABRs for treated spontaneous and traumatic joint bleeding episodes were 1.3 for patients with HA or HB and 0.0 for patients with HAwI or HBwI at the 56-week cut-off. **Conclusions:** Once-daily, subcutaneous concizumab prophylaxis resolved 86.3% of target joints in patients with HA or HB, and 91.8% of target joints in patients with HAwI or HBwI, most patients within 12.0 months. The median ABRs for treated spontaneous and traumatic target joint bleeding episodes at 56 weeks for both patients with HA or HB and HAwI or HBwI were 0.0.

Efficacy and Safety of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants with Severe Haemophilia without Inhibitors: Results from the Phase 3 Basis Trial (285)

https://ashpublications.org/blood/article/142/Supplement%201/285/501845/Efficacy-and-Safety-of-the-Anti-Tissue-Factor

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Introduction: In an oral presentation at the ASH Annual Meeting in December 2023, Matino et al evaluate the efficacy and safety of **marstacimab** in participants with severe HA or moderately severe to severe HB without inhibitors compared with previous factor replacement therapy. Marstacimab (PF-06741086) is a monoclonal antibody targeted to the tissue factor pathway inhibitor protein to improve hemostasis via the extrinsic pathway of blood coagulation. Previous phase 1/2 studies demonstrated the efficacy and safety of long-term administration of marstacimab up to 450 mg weekly for reducing bleeding episodes in adults with severe haemophilia A (HA) or haemophilia B (HB), with or without inhibitors, compared with on-demand (OD) therapy. **Methods:** BASIS (NCT03938792) is an open-label, multicenter, pivotal phase 3 study that enrolled male participants aged ≥12 to <75 y with severe HA (factor [F] VIII <1%) or moderately severe to severe (FIX ≤2%) HB, with or without inhibitors. Following screening, participants entered a 6-month observational phase (OP) and were categorized by factor replacement treatment: (1) OD or (2) routine prophylaxis (RP). Participants who completed the OP crossed over to 12-month active treatment phase (ATP) and received a single subcutaneous loading dose of 300 mg followed by once weekly 150 mg marstacimab. Primary endpoints were annualized bleeding rate (ABR) for treated bleeds and safety outcomes. Secondary endpoints included incidence of various types of breakthrough bleeds and health-related quality of life (HRQoL) measures. Participants who completed the ATP were eligible to enroll in the long-term extension (LTE) study. Informed consent/ethics committee approvals were obtained. Results for participants without inhibitors are presented. **Results**: Participants (N=128; 108 adults, 20 adolescents) with HA or HB without inhibitors entered the OP (OD: HA n=29, HB n=8; RP: n=72, HB n=19); of these, 116 entered the ATP. The median age was 30 [range, 13–66] y, most participants were White (50.8%) or Asian (47.7%) and predominately from Europe and India (51.6%). At baseline, 89 participants (69.5%; OD: n=36; RP: n=53) had ≥1 target joint. Mean (range) duration of marstacimab treatment was 12.1 (11.5–13.1) months for OD and 11.6 (0.9–12.8) months for RP. Eighty-eight participants entered the LTE (OD: HA n=22, HB n=7; RP: HA n=45; HB n=13). Data were not available by the cutoff date for 1 RP participant and was not included in the LTE safety analysis set. The mean (range) treatment duration in the LTE was 8.0 (1.2–14.5) months for OD and 6.5 (1.1–16.1) months for RP. In the phase 3 study, the OD group reported 12 (36.4%) adverse events (AEs) during ATP vs 9 (24.3%) in OP whereas the RP group reported 62 (74.7%) AEs in ATP vs 20 (22.0%) in OP. Both groups reported more treatment-related AEs during ATP. ADAs developed in 23/112 participants (20.5% incidence), of which titers were low and resolved in 22 participants by end of study. One RP participant discontinued due to a non-treatment-related SAE, and no deaths or thromboembolic events were recorded in the phase 3 study or the LTE. Mean (95% CI) ABR for treated bleeds was reduced for OD (91.6% [88.1–94.1%]) and RP (35.2% [5.6–55.6%]) participants over the 12-month ATP and marstacimab demonstrated superiority vs OD (P<0.001) and non-inferiority and superiority vs RP (P=0.0376) therapy. Marstacimab was also associated with significant reductions in ABR across all breakthrough bleed categories vs OD, and numerical reductions vs RP (non-inferiority). Overall, mean ABR declined over the first 6 months of ATP, which continued to Month 12 (data not shown). Bleed rates for an additional 16 months of follow-up in the LTE were consistent with those observed during the first 12 months of treatment in the phase 3 study. The ABR reductions observed with marstacimab during ATP were consistent across haemophilia types and age groups for OD and were generally consistent across haemophilia types and age groups for RP, with all point estimates for a difference <2.5 (non-inferiority margin for the ABR of treated bleeds). HRQoL parameters demonstrated non-significant improvements vs OD therapy and non-inferiority vs RP therapy. **Conclusion:** Compared with previous OD or RP therapy, once weekly subcutaneous marstacimab was safe and effective for reducing bleeding events in participants with severe HA or moderately severe to severe HB without inhibitors beyond 12 months in the phase 3 study and up to an additional 16 months in the LTE study.

Marstacimab, an Anti-Tissue Factor Pathway Inhibitor, in Participants with Haemophilia A or B, with and without Inhibitors: An Integrated Analysis of Safety (3980)

https://ashpublications.org/blood/article/142/Supplement%201/3980/501141/Marstacimab-an-Anti-Tissue-Factor-Pathway

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Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, Acharya et al report an integrated analysis of **marstacimab** safety in participants with HA or HB. Marstacimab (PF-06741086) targets tissue factor pathway inhibitor (TFPI) to restore hemostasis via the extrinsic pathway of blood coagulation. In phase 1/2 studies, long-term subcutaneous (SC) administration of marstacimab reduced bleeding episodes in adults with severe haemophilia A (HA) or haemophilia B (HB) (factor VIII or factor IX [FIX] <1%, respectively), with or without inhibitors. BASIS, the pivotal phase 3 study of marstacimab in adolescents and adults with severe HA (<1%) or moderately severe to severe (FIX ≤2%) HB, is ongoing. Given the potential risk for thrombotic and thromboembolic complications with novel non-factor-based agents, integrated safety analysis of studies of such agents are of interest. **Methods:** Data from participants in the phase 1b/2 study (NCT02974855), its long-term follow-up (LTFU; NCT03363321), the pivotal phase 3 BASIS study (NCT03938792), and its long-term extension (LTE; NCT05145127) were included. In the phase 1b/2 study, male participants (N=26) with severe HA or HB, with or without inhibitors, were assigned to escalating weekly SC doses of marstacimab based on inhibitor status (without inhibitors: 300 mg, a single 300-mg loading dose with subsequent 150-mg doses, or 450 mg; with inhibitors: 300 mg). In the BASIS study, male participants (N=163) with severe HA or moderately severe to severe HB, with or without inhibitors, received a single SC 300-mg loading dose followed by once-weekly 150 mg in the 12-month active treatment phase (ATP). Adverse events (AEs), serious adverse events (SAEs), and AEs of special interest (AESI), including thromboembolic events and injection site reactions (ISRs), were monitored. **Results**: Overall, 144 unique participants received marstacimab and were included in this analysis: 28 in the phase 1b/2 study (median treatment duration, 2.8 [range, 1.2–3.0] months) and its LTFU (15.0 [1.2–16.4] months) and 116 in the BASIS study (12.1 [0.9–13.1] months) and its LTE (6.4 [1.1–16.1] months; overall BASIS + LTE, 17.3 [0.9–28.2] months). There were no treatment-related SAEs in the phase 1b/2 study and 1 treatment-related SAE (peripheral swelling) in the BASIS study and its LTE. There were no deaths in any study. There were no AEs related to thromboembolism during treatment in participants with HA or HB across the marstacimab clinical program. Adverse drug reactions were consistent across studies. In the BASIS study and its LTE, ISRs (n=13, 11.2%) tended to be transient and mild in severity and did not lead to discontinuation from the study: other reactions were also mild: pruritus (n=4, 3.4%); rash (n=1, 0.9%) and headache (n=8, 6.9%). One participant, with a history of hemorrhoids, in the BASIS ATP had a grade 2 event of thrombosed hemorrhoids considered related to marstacimab (a local inflammation event, not related to any other thromboembolic event; dose was not interrupted or changed due to this event). No clinically important findings in laboratory values were associated with marstacimab. In the BASIS ATP, antidrug antibodies (ADAs) developed in 23/112 participants (20.5% incidence; titers were low and resolved in 22/23 participants by end of study); 6/23 were positive for neutralizing antibodies (NAbs; titers were transient and resolved by the end of study). In the LTE, ADA developed in 1/44 (2.3%) participants; the ADA titer was negative prior to marstacimab but positive at the end of the main study (titer = 2.48), positive at Day 180 in the LTE (titer = 2.41), and the participant tested negative for NAbs at both timepoints. No differences in the marstacimab safety profile, as determined by AEs, SAEs, AESIs, and discontinuations due to AEs, were reported in ADA positive or negative participants. Across the BASIS study and its LTE, 18 participants had a marstacimab dose escalation from 150 mg to 300 mg; 8/18 (44.4%) had AEs, all mild or moderate in severity and there were

no AEs or SAEs leading to treatment discontinuation. **Conclusion:** Once-weekly SC marstacimab was well tolerated in participants with severe HA or moderately severe to severe HB, without inhibitors, with a low rate and mild severity of ISRs, transient ADAs, and no thromboembolic events with continuous treatment up to 28 months in the phase 3 program.

Fitusiran Prophylaxis Demonstrates Sustained Bleed Protection in People with Haemophilia A or B: An Exploratory Analysis of Antithrombin Levels and Peak Thrombin Generation from Three Phase 3 Trials

https://doi.org/10.1016/j.rpth.2023.100232

Introduction: In an abstract published in Research and Practice in Thrombosis and Haemostasis in August 2023, Pipe et al explore the pharmacokinetics / pharmacodynamics of **fitusiran** prophylaxis through changes in AT levels and peak TG over time from three Phase 3 trials: ATLAS-INH, ATLAS-A/B and ATLAS PPX. Fitusiran, a subcutaneous (SC) investigational siRNA therapeutic, targets antithrombin (AT) to restore TG sufficient to rebalance hemostasis in people with haemophilia (PwH) A or B, with or without inhibitors. **Methods**: ATLAS-INH, ATLAS-A/B and ATLAS-PPX (NCT03417102, NCT03417245 and NCT03549871) were Phase 3, multinational, open-label trials that enrolled males aged ≥12 years with severe haemophilia A or B. In ATLAS-INH and ATLAS-A/B, PwH with or without inhibitors, respectively, were randomized 2:1 to once-monthly 80 mg fitusiran prophylaxis or on demand bypassing-agents (BPAs) (ATLASINH) or clotting factor concentrates (CFC) (ATLAS-A/B) for 9 months. In ATLAS-PPX, PwH with or without inhibitors who had prior CFC/BPA prophylaxis continued CFC/BPA prophylaxis for 6 months before switching to once-monthly 80 mg fitusiran prophylaxis for 7 months. The primary endpoint for all trials was annualized bleeding rate (ABR). Exploratory endpoints included change in AT levels and peak TG over time, both of which were assessed at monthly intervals. Safety and tolerability were also assessed. **Results**: Across the three trials, 187 participants received fitusiran prophylaxis (62 with inhibitors; 125 without). Median ABR was 0.0 in the fitusiran arm for all three trials. In PwH with inhibitors, there was a mean reduction in AT levels from baseline by 84.1% and 81.4% at Day 29 in ATLAS-INH and ATLAS-PPX, respectively. In PwH without inhibitors, there was a mean reduction in AT levels from baseline by 79.8% and 82.3% at Day 29 in ATLAS-A/B and ATLAS PPX, respectively. AT levels remained reduced during the entire study period in all three trials. In PwH with inhibitors, there was a mean increase in peak TG from baseline of 30.8 nM and 35.0 nM on Day 29 in ATLAS-INH and ATLAS PPX, respectively. In PwH without inhibitors, there was a mean increase in peak TG from baseline of 24.4 nM and 34.9 nM at Day 29 in ATLAS-A/B and ATLAS-PPX, respectively. TG remained elevated during the entire study period in all three trials. Reported adverse events were generally consistent with previously identified risks of fitusiran. **Conclusions**: Monthly 80 mg fitusiran prophylaxis met the target pharmacodynamic effect of AT lowering and increased peak TG by Day 29 (onset period) in PwH A or B, with or without inhibitors. These findings and low ABRs suggest fitusiran has the potential to rebalance hemostasis and provide sustained bleed protection in PwH A or B, irrespective of inhibitor status. A revised dose and dose regimen designed to improve the benefit-risk profile of fitusiran is under investigation in ongoing Phase 3 trials. The study was funded by Sanofi.

Antithrombin-lowering in Haemophilia: a Closer Look at Fitusiran

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In a *Review* article published in Research and Practice in Thrombosis and Haemostasis in May 2023, Young et al discuss the rationale for antithrombin (AT) lowering in individuals with haemophilia, with a focus on **fitusiran**, its mechanism of action, and its potential as a prophylactic therapy for individuals with haemophilia A or B, with or without inhibitors. Fitusiran is an investigational small interfering RNA

therapeutic for subcutaneous prophylaxis in individuals with haemophilia A or B, irrespective of their inhibitor status, that has the potential to be transformative in haemophilia management through rebalancing of thrombin generation resulting in a milder bleeding phenotype, impacting the quality of life and reducing overall treatment burden. Thrombin is a key enzyme in the maintenance of normal hemostatic function and is the central product of an interconnected set of simultaneously occurring cellular and proteolytic events. Antithrombin (AT) is a natural anticoagulant that downregulates different components of the clotting process, particularly thrombin generation. In good health, well-regulated hemostasis is the result of a balance between procoagulant and anticoagulant elements. Cumulative understanding of the regulation of thrombin generation and its central role in hemostasis and bleeding disorders has led to the clinical development of therapeutic strategies that aim to rebalance hemostasis in individuals with haemophilia and other coagulation factor deficiencies to improve bleeding phenotype. Ongoing clinical studies will provide further evidence on the efficacy and safety of fitusiran and its impact on patient-reported outcomes. It has been shown in preclinical in vitro and in silico studies that thrombin generation improves when fitusiran is added to plasma taken from patients with severe deficiency of FV, FVII, or FX. Owing to its mechanism of action and thrombin-targeted approach, fitusiran therefore may be of use in other rare bleeding disorders that arise from insufficient thrombin generation, but further clinical studies are needed to confirm this hypothesis. Overall, the evidence from clinical studies of fitusiran suggests that the benefits of the drug outweigh the risks and that fitusiran has the potential to change future clinical practice in haemophilia.

Fitusiran Population Pharmacokinetic and Pharmacodynamic Modeling Utilizing Phase 3 Clinical Trial Data to Confirm Doses Tested in Phase 3 Trials to Support an Antithrombin-Based Dose Regimen (2614)

https://ashpublications.org/blood/article/142/Supplement%201/2614/501770/Fitusiran-Population-Pharmacokinetic-and

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Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, Madrasi et al present an updated **fitusiran** PopPK/PD model using pooled Phase 1/2 and Phase 3 AT activity data to guide an AT-based dose regimen for Phase 3 trials in adults with haemophilia. Fitusiran is an investigational siRNA therapeutic designed to target antithrombin (AT) with the goal of rebalancing hemostasis in people with haemophilia (PwH) A or B, regardless of inhibitor status. A semi-mechanistic population pharmacokinetic / pharmacodynamic (PopPK/PD) model using Phase 1/2 data from 1000 virtual PwH was previously developed to inform dose selection for the Phase 3 program using a fitusiran AT-based dosing regimen. This indicated that a starting dose of 50 mg once every 2 months (Q2M) would maintain AT activity between 15–35% for a considerable number of PwH, and aim to mitigate the risk of thrombosis and preserve bleed control. **Methods:** Plasma AT activity data from Phase 1 (NCT02035605), Phase 1/2 (NCT02554773) and Phase 3 studies (NCT03417102, NCT03417245, NCT03549871) in PwH A/B, with or without inhibitors were pooled to update the PopPK/PD model. Pooled AT activity data generated a large dataset with diverse populations and allowed for the evaluation of potential effects of intrinsic and/or extrinsic factors as covariates on AT activity in the targeted haemophilia population. The final PopPK/PD model was used to simulate AT activity at various dosing regimens in 1500 virtual PwH to select the final AT-based dosing regimen. **Results:** The PopPK/PD dataset included 44059 AT activity observations from 339 participants. An indirect response model well described the dynamics of AT activity and intra-individual variability. The covariate effects identified in the PopPK/PD model were White race on Kout (increase in elimination rate of AT) and half maximal inhibitory concentration (IC50; increase in model derived potency estimate), bodyweight on Kout (increase with bodyweight), age with IC50 (increase with

age). Simulations predict that with a starting dose of 50 mg Q2M, >58% of PwH would achieve AT activity >15% (10th percentile trough-AT activity was 15.3%). Mean peak AT activity is projected to be 24.7 ± 10%. For PwH with >35% AT activity, a dose escalation to 50 mg every month (QM) would be required to achieve target AT activity <35%. It is predicted that 0.8% of PwH would then be escalated to 80mg QM in a stepwise manner. With the starting dose of 50 mg Q2M, 41.7% of PwH are predicted to have AT activity <15%; these PwH should be de-escalated to 20 mg Q2M. At a dose of 20 mg Q2M, 10.2% would have AT activity <15%. **Conclusions:** PopPK/PD model simulations confirm that the fitusiran AT-based dose regimen with a starting dose of 50 mg Q2M that can be escalated or de-escalated maintains the target AT range of 15–35% in the majority of PwH. It is predicted approximately 88% of PwH will require zero or one dose change. The efficacy and safety of the fitusiran AT-based dose regimen is being evaluated in ongoing clinical trials.

Serpin-PC in Persons with Severe Haemophilia (PwH): Updated Results from a Multicenter Multi-Part, First-in-Human Study (2619)

https://ashpublications.org/blood/article/142/Supplement%201/2619/500147/Serpin-PC-in-Persons-with-Severe-Haemophilia-PwH

Blood (2023) 142 (Supplement 1): 2619. https://doi.org/10.1182/blood-2023-179969

Introduction: In a poster and abstract at the ASH Annual Meeting in December 2023, Baglin et al previously presented data from the completed parts of AP-0101 showing that administration of SerpinPC reduced bleeding in persons with severe haemophilia with no observations of unexplained chronic elevation in D-dimer. They now present all results up to the end of Part 5 by which time they anticipate the median continuous exposure will be more than 3 years. SerpinPC is an investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit Activated Protein C (APC). **Methods:** AP-0101 is an ongoing first-in-human open-label multicenter study utilizing an adaptive design to investigate the safety, tolerability, pharmacokinetics and efficacy of SerpinPC in subjects with severe haemophilia A and B. Part 1a was a Single Ascending Dose Study of SerpinPC in 15 healthy male volunteers and 12 males with severe haemophilia. Part 2 enrolled 23 males with severe haemophilia (19 haemophilia A and 4 haemophilia B), who were not on replacement factor prophylaxis, to receive SerpinPC at 0.3, 0.6 or 1.2 mg/kg, administered as a subcutaneous (SC) injection once every 4 weeks over a 24-week period (6 total doses). In Part 3, subjects who completed Part 2 received a flat dose of 60 mg of SerpinPC once every 4 weeks for 48 weeks. Part 4 was a further extension in which subjects who completed Part 3 received 1.2 mg/kg of SerpinPC once every 2 weeks for 24 weeks. Part 5 was a further extension in which subjects who completed Part 4 continued to receive 1.2 mg/kg of SerpinPC once every 2 weeks for 52 weeks. **Results:** Annualized bleed rates, safety and tolerability for Part 5 will be available and a complete summary of all results to the end of Part 5 will be presented, including available pharmacokinetic and anti-drug antibody data. The lead author is an employee of Centessa Pharmaceuticals.

VON WILLEBRAND DISEASE AND OTHER RARE BLEEDING DISORDERS

The von Willebrand Factor-binding Aptamer Rondaptivon Pegol as a Treatment for Severe and Non-severe Haemophilia A

https://pubmed.ncbi.nlm.nih.gov/36108308/

Blood. 2023 Mar 9;141(10):1147-1158. doi: 10.1182/blood.2022016571.

Introduction: In a paper published in Blood in March 2023, Ay et al assessed the safety, pharmacokinetics, and pharmacodynamics of **rondaptivon pegol (BT200)** in haemophilia A. Factor VIII circulates in a noncovalent complex with von Willebrand Factor (VWF), the latter determining FVIII half-life. The VWF-binding aptamer rondaptivon pegol (BT200) increases plasma levels of VWF/FVIII in healthy volunteers. **Methods**: Nineteen adult patients (ages 20-62 years, 4 women) with haemophilia A (8 mild, 2 moderate, and 9 severe) received subcutaneous injections of rondaptivon pegol. After an initial fixed dose of 3 mg on days 0 and 4, patients received weekly doses of 2 to 9 mg until day 28. Severe haemophilia A patients underwent sparse-sampling population pharmacokinetics individual profiling after the final dose of rondaptivon pegol. Adverse events, pharmacokinetics, and pharmacodynamics were assessed. FVIII activity and VWF levels were measured. **Results**: All patients tolerated rondaptivon pegol well. The geometric mean half-life of rondaptivon pegol was 5.4 days and rondaptivon pegol significantly increased VWF levels. In severe haemophilia A, 6 doses of rondaptivon pegol increased the half-lives of 5 different FVIII products from a median of 10.4 hours to 31.1 hours (range, 20.8-56.0 hours). Median FVIII increased from 22% to 48% in mild haemophilia A and from 3% to 7.5% in moderate haemophilia A. **Conclusions**: Rondaptivon pegol is a first-in-class pro-hemostatic molecule that extended the half-life of substituted FVIII approximately 3-fold and increased endogenous FVIII levels approximately 2-fold in haemophilia patients. This trial was registered at www.clinicaltrials.gov as #NCT04677803.

Study to Assess the Pharmacokinetics and Safety and Tolerability of Efanesoctocog Alfa (BIVV001)in Adults with Type 2N and 3 Von Willebrand Disease (VWD)

https://www.sanofistudies.com/us/en/listing/286387/to-assess-the-pharmacokinetics-and-safety-and-tolerability-of-efanesoctocog-alfa-bivv001in-adults-with-type-2n-and-3-von-willebrand-disease-vwd/

In July 2023, Sanofi announced a study to characterize the pharmacokinetics (PK) of **Efanesoctocog Alfa** (**BIVV001**, brand name **Altuviiio**) after a single intravenous (IV) administration, as assessed by factor VIII (FVIII) activity determined by the one-stage activated partial thromboplastin time (aPPT) clotting assay, as well as, BIVV001 capture chromogenic Coatest FVIII activity assay, and to assess the safety and tolerability of a single IV dose of BIVV001 in adult patients with type 2N and 3 VWD. The total study duration is up to 57 days: screening of up to 28 days followed by up to 29 days of safety observation following the IV BIVV001 dose administration. Eligibility criteria include von Willebrand disease (VWD), age between 18 and 65 years, male or female.

Vega Therapeutics Commences VGA039 Clinical Trial to Treat VWD

https://www.clinicaltrialsarena.com/news/vega-vga039-clinical-trial/?cf-view

In April 2023, clinical stage biotechnology firm Vega Therapeutics announced a clinical trial to assess **VGA039**, an anti-protein S monoclonal antibody, in the treatment of von Willebrand disease (VWD). The company has dosed the first participant in the multinational Phase I clinical trial of this first-in-class antibody therapy, VGA039. The trial has been designed for evaluating the tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and safety of VGA039 after single IV or SC dose administration in healthy participants and single SC dose administration in VWD patients. It is being conducted after the receipt of the investigational new drug application (IND) approval by the US Food and Drug Administration (FDA) and clinical trial application (CTA) approval in Europe. The company stated that the trial will commence enrolment of healthy volunteers and will expand to include VWD patients.

Hemab Therapeutics Announces First Patient Dosed in Phase 2 Clinical Study Investigating HMB-001 for the Treatment of Glanzmann Thrombasthenia

https://www.prnewswire.com/news-releases/hemab-therapeutics-announces-first-patient-dosed-in-phase-2-clinical-study-investigating-hmb-001-for-the-treatment-of-glanzmann-thrombasthenia-302010811.html

In December 2023, Hemab Therapeutics, a clinical-stage biotechnology company developing novel prophylactic therapeutics for serious, underserved bleeding and thrombotic disorders, announced that it had completed Phase 1, the single ascending dose part, and transitioned to Phase 2, the multiple ascending dose part, of its Phase 1/2 clinical study of HMB-001 in Glanzmann Thrombasthenia (GT), a platelet disorder that causes severe, potentially life-threatening bleeding episodes. HMB-001 is a novel bispecific antibody designed to be the first prophylactic treatment for Glanzmann Thrombasthenia (GT) and other debilitating bleeding disorders. Phase 1 was successfully completed in the UK; Hemab plans additional sites in Europe and the U.S. for Phase 2. The U.S. FDA has cleared the Investigational New Drug (IND) application and granted Fast Track Designation to HMB-001 for the treatment of GT. The Phase 1/2 clinical study evaluates the safety, tolerability, pharmacodynamics, and pharmacokinetics of HMB-001. Initial efficacy signals based on an assessment of changes in bleeding frequency will also be measured. The study is composed of three parts: Part A, single ascending dose, Part B, multiple ascending dose, and Part C, extended dosing. Hemab plans to report data from the Phase 1, single ascending dose portion, at an international scientific conference in early 2024.

FACTOR REPLACEMENT THERAPIES IN DEVELOPMENT and/or UNDER HTA REVIEW						
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Replacement FVIII	**Haemophilia A**	BIVV001	Efanesococog alfa (rFVIIIFc-VWFD'D3-XTEN), SHL	Intravenous	Sanofi and Sobi co-development	**Phase 3 completed, Licensed in US and Japan**

BISPECIFIC MONOCLONAL ANTIBODIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Bi-specific monoclonal antibody	**Haemophilia A**	Mim8	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Novo Nordisk	**Phase 3**
Bi-specific monoclonal antibody	**Haemophilia A**	NXT007	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Chugai	**Phase 1/2**
Bi-specific monoclonal antibody	**Glanzmann Thrombasthenia**	HMB-001	Bispecific antibody binding to FVIIa and TLT-1	Subcutaneous	Hemab	**Phase 1/2**

RE-BALANCING AGENTS (NON-REPLACEMENT THERAPIES) IN DEVELOPMENT and/or UNDER HTA REVIEW						
NRT monoclonal antibody, Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	Concizumab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Novo Nordisk	**Phase 3 (approved for PHABwI) in Canada, Australia, Japan)**
NRT monoclonal antibody, Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	Marstacimab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Pfizer	**Phase 3**
NRT siRNA	**Haemophilia A or B w/ or**	Fitusiran	Antithrombin Small interfering (si)RNA to down-regulate antithrombin	Subcutaneous	Sanofi	**Phase 3**

	w/o inhibitors					
NRT Activated Protein C inhibitor	**Haemophilia A or B w/ or w/o inhibitors**	SerpinPC	Activated Protein C inhibitor	Subcutaneous	Apcintex	**Phase 1/2 Received FDA Orphan Drug Designation for HB**
Aptamer	**Haemophilia A, type 2B VWD**	Rondoroptivon pegol BT200	Pegylated aptamer binding to vWF	Subcutaneous	Medical University of Vienna	**Phase 2**

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**	Roctavian™ Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	Single intravenous infusion	BioMarin	**Conditional marketing authorisation in Europe (brand name Roctavian™), approved by U.S. FDA**
Gene Therapy	**Haemophilia A**	PF-07055480 giroctocogene fitelparvovec (formerly SB-525)	Gene therapy using a rAAV2/6 vector, encoding the B-domain deleted human FVIII	Single intravenous infusion	Pfizer (originally Sangamo)	**Phase 3**
Gene Therapy	**Haemophilia A**	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Single intravenous infusion	Bayer	**Phase 1/2**
Gene Therapy	**Haemophilia A**	dirloctogene samoparvovec, SPK-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Single intravenous infusion	Roche, formerly Spark	**Phase 3**

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 bioengineered human FVIII (ET3) transgene.	Single intravenous infusion	ASC Therapeutics	**Phase 1/2**
Gene Therapy	**Haemophilia A**	CD68-ET3-LV-CD34+	CD34+ hematopoietic stem cells transduced with CD68-ET3 Lentiviral vector (encoding human factor VIII gene) is administered by IV infusion following conditioning regimen	Single intravenous infusion	Christian Medical College, Vellore, India	**Phase 1**
Gene Therapy	**Haemophilia B**	PF-06838435	Padua variant	Single intravenous infusion	Pfizer (Originally Spark)	**Phase 3, approved in Canada (brand name BEQVEZ)**

		fidanacogene elaparvovec (formerly SPK-9001)	(rAAV-Spark100) (fidanacogene elaparvovec)			
Gene Therapy	**Haemophilia B**	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	Single intravenous infusion	**CSL Behring (formerly uniQure)**	**Licensed U.S. and Canada and conditional marketing authorization 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**

CELL-BASED THERAPIES IN DEVELOPMENT

Type of product	Indication / treatment of	Product name(s)	Name(s) of active ingredient	Mode of administration	Developer / manufacturer	Development stage
Cell-based therapy	**Haemophilia A with inhibitors**	TI-168	Autologous FVIII TCR-Treg cell therapy	-	TeraImmune Inc.	**Phase 1/2a clinical trial planned for 2024, Orphan drug status granted by FDA**

LICENSED FACTOR REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	**VWD**	Veyvondi® Vonvendi®	rVWF (vonicog alfa)	Takeda	**Licensed**
Replacement VWF/FVIII	**VWD Haemophilia A**	Voncento®	human coagulation factor VIII & human von Willebrand factor	CSL Behring	**Licensed**
Replacement VWF/FVIII	**VWD Haemophilia A**	Haemate P®	human coagulation FVIII & human von Willebrand factor	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Advate®	human coagulation factor VIII (rDNA), octocog alfa, SHL	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Adynovi® Adynovate® BAX855 TAK-660 SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol), EHL	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Afstyla® CSL627	rVIII-Single Chain, SHL	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Elocta® Eloctate®	rFVIIIFc (efmoroctocog alfa), EHL	Sobi	**Licensed**

Replacement FVIII	**Haemophilia A**	Esperoct® N8-GP	rFVIII glycoPEGylated (turoctocog alfa pegol), EHL	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Jivi® BAY 94-9027	rFVIII (damoctocog alfa pegol), EHL	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kogenate® FS	Recombinant FVIII, SHL	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kovaltry® BAY 81-8937	unmodified full-length rFVIII (octocog alfa), SHL	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Novoeight®	rFVIII (turoctocog alfa), SHL	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Nuwiq®	human-cell-line-recombinant-human-FVIII (simoctocog alfa human-cl-rhFVIII), SHL	Octapharma	**Licensed**
Replacement FVIII	**Haemophilia A**	Refacto AF®	moroctocog alfa, SHL	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Alprolix®	rFIXFc (eftrenonacog alfa), EHL	Sobi	**Licensed**
Replacement FIX	**Haemophilia B**	BeneFIX®	nonacog alfa, SHL	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Idelvion®	rFIX-FP / recombinant factor IX albumin fusion protein, EHL	CSL Behring	**Licensed**

Replacement FIX	**Haemophilia B**	Refixia® / Rebinyn® rFIX-GP / N9-GP	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol), EHL	Novo Nordisk	**Licensed**
Replacement FIX	**Haemophilia B**	RIXubis®	Nonacog gamma, SHL	Takeda	**Licensed**
Replacement FXIII	**Factor XIII deficiency**	NovoThirteen®/ Tretten	Recombinant FXIII (catridecacog)	Novo Nordisk	**Licensed**

LICENSED FVIII MIMETICS						
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**	Hemlibra	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Roche	**Licensed in US and Europe**

LICENSED BYPASSING AGENTS					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	Sevenfact®/ Cevenfacta®	Recombinant FVIIa- jncw	LFB	**Licensed in the US and Mexico (under brand name Sevenfact®) Licensed in Europe and the UK under brand name Cevenfacta®**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	NovoSeven® / NovoSeven® RT	Recombinant FVIIa (eptacog alfa)	Novo Nordisk	**Licensed**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	FEIBA	Anti-Inhibitor Coagulant Complex approved for use in hemophilia A and B patients with inhibitors	Takeda	**Licensed**
Bypassing agent	**Acquired haemophilia A**	Obizur®	Antihemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA	Takeda	**Licensed**

			derived, antihemophilic factor indicated for the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A		

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	**Licensed in US and conditional marketing authorization 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 conditional marketing authorization in Europe**
Gene Therapy	**Haemophilia B**	BEQVEZ® PF-06838435 fidanacogene elaparvovec (formerly SPK-9001)	Padua variant (rAAV-Spark100) (fidanacogene elaparvovec)	Pfizer	**Licensed in Canada (brand name BEQVEZ)**