EHC
european haemophilia consortium

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

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Inhibitors Only

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FOREWORD

Welcome to a new edition of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia and other rare bleeding disorders.

In this edition, we primarily cover news from the 2020 World Federation of Hemophilia (WFH) Virtual Summit, held in June 2020, and the International Society on Thrombosis and Haemostasis (ISTH) Virtual Congress, held in July 2020 as well as other industry updates and news in general. The abstracts of the WFH and ISTH meetings can be accessed online. For your convenience, we also include a table on all treatments covered in this newsletter as well as other novel treatment under development. We hope this will facilitate your understanding of the therapeutic landscape.

The purpose of this newsletter is to provide both up-to-date information to EHC National Member Organisations (NMOs), and a general overview and understanding of a rapidly evolving landscape of medicinal product developments in rare bleeding disorders. The EHC encourages its NMOs to adapt this newsletter to their national needs but takes no responsibility for any changes.

This newsletter provides information by specific type of disorder: haemophilia A and B; inhibitors in haemophilia, von Willebrand disease, and other rare bleeding disorders.

The EHC wishes to thank its New Products Working Group, which has overseen the content and production of this newsletter. Its members include:

- Dr. Mariëtte Driessens, EHC volunteer,
- Dr. Radoslaw Kaczmarek, Medical and Scientific Advisory Group (MASAG) member,
- Dr. Dan Hart, EHC MASAG member,
- Dr. Ilmar Kruis, EHC volunteer,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) Chair,
- Mr. Declan Noone, EHC President,
- Asst. Prof. Brian O'Mahony, MASAG member,
- Mr. David Page, Canadian Hemophilia Society,
- Prof. Flora Peyvandi, EHC Medical Advisory Group (MAG) member,
- Geneviève Piétu, PhD, EHC volunteer,
- Ms. Laura Savini, EHC Public Policy and Communications Officer,
- Dr. Uwe Schlenkrich, EHC volunteer.

The EHC welcomes all treatment developments that may benefit patients in the future. The EHC takes no position on any product type or class reported in this newsletter. This document does not intend to replace the medical advice provided by healthcare professionals.

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

Sincere regards,

Declan Noone
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

AAV:	Adeno-associated viral
ABD:	Albumin binding domains
ABR:	Annualised bleeding rate
AE:	Adverse events
AUC:	Area under the curve
aPCC:	Activated prothrombin complex concentrate
BPA:	Bypassing agents
BU/ml:	Bethesda units per millilitre
CBDR:	Canadian Bleeding Disorders Registry
CT:	Clinical trial
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
FIX:	Factor IX
FVIII:	Factor VIII
gc/Kg:	Genome copies per kilogram
h:	Human
HA:	Haemophilia A
HAwI:	Haemophilia A with inhibitors
HB:	Haemophilia B
HBwI:	Haemophilia B with inhibitors
HCP:	Healthcare professionals
HJHS:	Haemophilia Joint Health Score
IQR:	Interquartile Range
ISTH:	International Society on Thrombosis and Haemostasis
IU:	International units
IU/dl:	International units per decilitre
IU/kg:	International units per kilogram
n=:	Number
NAb:	Neutralizing antibodies
NHP:	Non-human primates
pd:	plasma-derived
PK:	Pharmacokinetics
PPX:	Prophylaxis
PwHA:	Person with haemophilia A
PwHB:	Person with haemophilia B
r:	recombinant
rFVIIa:	recombinant activated factor VII
RNA:	Ribonucleic acid

SAE:	Serious adverse events
SQ:	Subcutaneous
UK:	United Kingdom
US:	United States
vg/Kg:	Vector genomes per kilogram
vs:	versus
VWD:	von Willebrand disease
VWF:	von Willebrand factor
WFH:	World Federation of Hemophilia
µg/kg:	microgram per kilogram

AN UPDATE ON NOVEL TREATMENTS FOR PEOPLE WITH HAEMOPHILIA A AND B AND INHIBITORS

Bypassing agents

Treatment of acute bleeds with MarzAA

Catalyst Biosciences presented two posters at the ISTH Virtual Congress on their new recombinant FVIIa product. The first poster, "Phase I study to evaluate the PK, pharmacodynamics, and safety of ascending doses of subcutaneous (SQ) **marzeptacog alfa** (**activated**) (**MarzAA**) in adult patients with haemophilia" included the final data from *MAA-102*. This study was conducted in adults with haemophilia A or B, with or without inhibitors, to evaluate the PK, pharmacodynamics, and safety of a single intravenous dose and ascending SQ (single and multiple) doses of MarzAA. The final data demonstrated the potential of SQ MarzAA to rapidly achieve and maintain therapeutic levels to treat acute bleeding events in haemophilia and confirm the dosing regimen chosen for the upcoming phase III trial, *Crimson 1*.

The second poster: "Marzeptacog alfa (activated) population PK: Simulations for dose selection in Phase 3 trials" was a population PK model developed and used for simulations of clinical trials. Based on simulating PK for SQ MarzAA in 1000 patients, the model confirmed that target levels for haemostasis may be rapidly achieved and sustained for over 24 hours in the upcoming phase III *Crimson 1* trial using 60 µg/kg dosed SQ once, and 36-48 hours when dosed twice or three times at 3-hour intervals.

Additionally, Catalyst Biosciences announced the design for the pivotal phase III *Crimson 1* ("Subcutaneous Marzeptacog Alfa (Activated) For On Demand Treatment and Control of Bleeding Episodes in patients with Haemophilia A or Haemophilia B with Inhibitors") study that will enrol individuals who experience episodic bleeding (NCT04489537). *Crimson 1* will be a cross-over, open-label global trial, evaluating the safety and efficacy of SQ MarzAA in the treatment of approximately 244 bleeding episodes in approximately 60 patients, compared with standard of care in a similar number of bleeding episodes. The study will assess the effectiveness of SQ MarzAA, using up to three doses to treat a bleeding episode. The primary endpoint will be haemostatic efficacy at 24 hours using a standard four-point assessment scale.

Non-replacement therapies

Comparison of bypassing agents in patients using Hemlibra®

In an abstract (PB1148) at the ISTH Virtual Congress, researchers aimed to assess the effect on thrombin generation by spiking various concentrations of BPAs on plasma taken from patients on **Hemlibra®**. Management of breakthrough bleeding events in inhibitor patients on Hemlibra® involves episodic treatment with activated prothrombin complex concentrate (aPCC) and recombinant activated FVII (rFVIIa). A concomitant drug reaction between Hemlibra® and aPCC resulting in thrombotic events was noted as a SAE in the *HAVEN* CTs. Eleven patients with severe HA and inhibitors currently on Hemlibra® for at least six weeks were enrolled in the study. The thrombin generation assay parameters were assessed.

In conclusion, it was demonstrated that lower doses of aPCC could potentially be used safely and effectively in inhibitor patients on Hemlibra®. It would be important to test this hypothesis in a clinical study.

Inhibitor status of patients with haemophilia A who transitioned to Hemlibra® after ITI

Researchers from Emory University (WFH Virtual Summit abstract MED-FP-011 (139)) evaluated the inhibitor status of patients with haemophilia A and a history of inhibitors successfully or partially tolerized after immune tolerance induction (ITI) who have switched from FVIII prophylaxis to **Hemlibra®.** The medical records of paediatric patients with haemophilia A and inhibitor history (N.B. duration of inhibitor not specified) on Hemlibra® were evaluated. Half of the eight patients evaluated in this study had a history of a high titre inhibitor (range 1.7-819 BU/mL). Three patients had been successfully tolerized and five patients achieved partial tolerance after ITI. Six patients (75%) transitioned to Hemlibra® alone while two patients (25%) transitioned to Hemlibra® with intermittent FVIII dosing. In the group of six patients on Hemlibra® alone, one patient had a peak inhibitor titre at 2.5 chromogenic BU/mL five months after starting Hemlibra®. However, three of the five patients with a negative inhibitor titre had positive anti-FVIII IgG4 antibodies. Both of the patients on Hemlibra® and intermittent FVIII dosing were partially tolerized and had negative inhibitor titres, but positive anti-FVIII IgG4 antibodies. FVIII dosing regimens for patients on Hemlibra® and intermittent FVIII exposure was prescribed as 50 IU/kg twice weekly or once every other week infusions. None of the patients had detectable anti-FVIII IgG1 antibodies.

The majority of patients maintained negative inhibitor titres after switching to Hemlibra® with or without intermittent FVIII exposure. However, the persistence of anti-FVIII IgG4 antibodies raises concern for an underlying inhibitor that could result in a re-occurrence of the inhibitor following intense factor exposure for example due to a catastrophic bleed and major surgery.

Preliminary report from major orthopaedic surgeries with Hemlibra® and rFVIIa

Researchers from Florence, Italy (WFH Virtual Summit abstract MED-PP-025 (101)) reported their experience in major orthopaedic surgery in PwHA and inhibitors on **Hemlibra®.**

For many years, PwHA and inhibitors needing surgery have been treated by using aPCC or rFVIIa. Hemlibra® was used together with rFVIIa because of the thrombotic risk associated with the use of aPCC and Hemlibra®. Between 2018 and 2019, three PwHA and high titre inhibitors underwent four major orthopaedic surgeries: one amputation above the knee and a total knee arthroplasty in a 56-year-old patient; a total hip arthroplasty in a 59-year-old patient; and a partial revision knee arthroplasty in a 49-year-old patient. All patients were previously managed for surgery by rFVIIa prophylaxis. Parameters of evaluation were: pain visual analogue scale (VAS), HJHS, and radiologic study. Hemlibra® was continued once weekly and they were treated before and after surgery by bolus infusions of rFVIIa (90 µg/kg) every four hours during the first two days, every six hours the next two days after surgery, every eight hours for an additional two days, and then with longer intervals, up to two weeks.

All patients were successfully managed by a single surgeon, without any complications during surgery, the postoperative period, and at the latest follow-up. The mean follow-up was 15.3 months (range: 5-22). Effective bleeding control was confirmed during surgery. No AEs were observed for the haematological prophylaxis, and in particular, no significant changes of markers of thrombophilia/microangiopathy were observed. All patients were regularly discharged after early rehabilitation with a mean hospital stay of 12.1 days (range: 12-13); they were then admitted to the rehabilitative ward at the same hospital.

All patients reported satisfaction for pain reduction and improved joint and global function as per VAS and HJHS scores.

Researchers concluded that major orthopaedic surgery with a regimen of Hemlibra® and rFVIIa in PwHA and inhibitors has been efficaciously performed with successful clinical outcome and effective bleeding control. This represents the first series of major orthopaedic surgeries ever reported in this setting. However, a larger number of procedures are required in order to validate this haematological protocol for orthopaedic surgery.

REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	**VWD**	Veyvondi Vonvendi	rVWF (vonicog alfa)	Takeda	**Licensed**
Replacement VWF plasma-derived	**VWD** **Haemophilia A**	Voncento	human coagulation factor VIII & human von willebrand factor	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Advate	human coagulation factor VIII (rDNA), octocog alfa	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Adynovi Adynovate BAX855 TAK-660 SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Afstyla CSL627	rVIII-Single Chain	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Elocta Eloctate	rFVIIIFc (efmoroctocog alfa)	Sobi	**Licensed**
Replacement FVIII	**Haemophilia A**	Esperoct N8-GP NNC 0129-0000-1003	rFVIII (turoctocog alfa pegol)	Novo Nordisk	**Licensed**

Replacement FVIII	**Haemophilia A**	Jivi BAY 94-9027	rFVIII (damoctocog alfa pegol)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kovaltry BAY 81-8937	unmodified full-length rFVIII (octocog alfa)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Novoeight®	turoctocog alfa	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Nuwiq	human-cell-line-recombinant-human-FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	**Licensed**
Replacement FVIII	**Haemophilia A**	Refacto AF	moroctocog alfa	Pfizer	**Licensed**
Replacement FVIII	**Haemophilia A**	BIVV001	rFVIIIFc-VWFD'D3-XTEN	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Alprolix	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**
Replacement FIX	**Haemophilia B**	BeneflX	nonacog alfa	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Idelvion	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	**Licensed**

Replacement FIX	**Haemophilia B**	Refixia / Rebinyn	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	**Licensed**
Replacement FIX	**Haemophilia B**	RIXubis	Nonacog gamma	Takeda	**Licensed**
Replacement FIX	**Haemophilia B**	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Catalyst Bioscience	**Phase 2**

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/[1] inhibitors**	Sevenfact	Recombinant FVIIa- jncw	LFB	**Licensed in the US**
Bypassing agent	**Haemophilia A or B w/ or w/o[2] inhibitors**	Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**

[1] w/: with

[2] w/o: without

NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Non-replacement therapy (NRT) Bispecific antibody	**Haemophilia A w/ or w/o inhibitors**	Hemlibra emicizumab ACE-910	Bispecific antibody	Roche	**Licensed**
NRT Bispecific antibody	**Haemophilia A**	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**
NRT Bispecific antibody	**Haemophilia A**	F1049	Bispecific antibody	Kymab	**Pre-clinical studies**
NRT bispecific antibody	**Haemophilia A**	NXT004 to NXT007	Bispecific antibody	Chugai	**Pre-clinical studies**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	Concizumab	Anti-TFPI	Novo Nordisk	**Phase 3 trials resumed**[3]
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	BAY 1093884	Anti-TFPI	Bayer	**Phase 2 trial terminated due to thrombosis**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	PF-06741086 Marstacimab	Anti-TFPI	Pfizer	**Phase 3 dosing started**

[3] Text in red indicates changes in the table since the last issue.

NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	MG1113	Anti-TFPI	Green Cross	**Phase 1**
NRT siRNA	**Haemophilia A or B w/ or w/o inhibitors**	Fitusiran	Antithrombin Small interfering (si)RNA	Sanofi Genzyme	**global dosing hold**
NRT Activated Protein C inhibitor	**Haemophilia A or B w/ or w/o inhibitors**	SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1/2**

GENE THERAPY					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Roctavian® Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	**Withheld approval**
Gene Therapy	**Haemophilia A**	SB-525 giroctocogene fitelparvovec	Gene therapy using a rAAV2/6 vector	Pfizer (originally Sangamo)	**Phase 3**
Gene Therapy	**Haemophilia A**	BAY-2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
Gene Therapy	**Haemophilia A**	Spark-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Spark	**Phase 1/2**

Gene Therapy	**Haemophilia A**	TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Clinical trial suspended**
Gene Therapy	**Haemophilia A**	AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	UCL/St. Jude	**Phase 1**
Gene Therapy	**Haemophilia A**	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Expression Therapeutics	**Phase 1**
Gene Therapy	**Haemophilia A**	Spark-8016	Recombinant AAV composed of a liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia A**	YUVA-GT-F801	autologous HSC/MSC modified with lentivirus encoding FVIII	SGIMI	**Phase 1**
Gene Therapy	**Haemophilia A**	AMT-180	Gene therapy using an AAV5-based gene therapy using a FIX variant (FIX-FIAV)	uniQure	**Clinical programme deprioritised**
Gene Therapy	**Haemophilia B**	PF-06838435 fidanacogene elaparvovec	Padua variant (AAV-Spark100) (fidanacogene elaparvovec)	Pfizer (Originally developed by Spark Therapeutics)	**Phase 3**

		(formerly SPK-9001)			
Gene Therapy	**Haemophilia B**	AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	uniQure	**Phase 3**
Gene Therapy	**Haemophilia B**	AMT-060	Gene therapy using AAV5 vector encoding FIX	uniQure	**Phase 1/2**
Gene Therapy	**Haemophilia B**	SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene into albumin locus	Sangamo	**Phase 1/2**
Gene Therapy	**Haemophilia B**	FLT180a	AAV encoding FIX Padua variant	Freeline	**Phase 1/2**
Gene Therapy	**Haemophilia B**	AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	SJCRH	**Phase 1**
Gene Therapy	**Haemophilia B**	YUVA-GT-F901	autologous HSC/MSC, modified with lentivirus encoding FIX	SGIMI	**Phase 1**
Gene Therapy	**Haemophilia B**	CB2679d-GT	Novel chimeric AAV vector Delivering an enhanced potency FIX	Catalyst Biosciences	**Pre-clinical studies**

Gene Therapy	**Haemophilia B**	TAK-748 (formerly SHP648/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Takeda	**Clinical trial suspended**

CELL-BASED THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	**Haemophilia A**	SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Phase 1/2**