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

2020 Issue One

Inhibitors Only

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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.

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 2019 Congress of the American Society of Hematology (ASH) and the 2020 Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) as well as other news from the industry and from the news in general. The abstracts of the EAHAD congress can be accessed online here. For your convenience, we have also decided to 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 use and 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, EHC Steering Committee member,
- Dr. Dan Hart, EHC Medical and Scientific Advisory Group (MASAG) member,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) Chair,
- Mr. Declan Noone, EHC President,
- Asst. Prof. Brian O'Mahony, MASAG member,
- Mr. David Page, EHC volunteer,
- Prof. Flora Peyvandi, EHC Medical Advisory Group (MAG) member,
- Dr. Geneviève Piétu, EHC volunteer,
- Ms. Laura Savini, EHC Public Policy and Communications Officer,
- Dr. Uwe Schlenkrich, EHC volunteer, and
- Dr. Ilmar Kruis, 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

AJBR:	Annualised joint bleeding rate
ABR:	Annualised bleeding rate
AE:	Adverse events
aPCC:	Activated prothrombin complex concentrate
aPTT:	Activated partial thromboplastin time
ASH:	American Society of Hematology
BPA:	Bypassing agents
BU/ml:	Bethesda units per millilitre
CI:	Confidence interval
ED:	Exposure day
EHL:	Extended half-life
ER:	Emergency room
EU:	European Union
F:	Factor
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
HCV:	Hepatitis C
HEAD-US:	Haemophilia early arthropathy detection with ultrasound
Hemo-QoL-A:	Haemophilia specific quality of life questionnaire
HIV:	Human Immunodeficiency Virus
Hrs:	Hours
IQR:	Interquartile Range

ITI:	Immune tolerance induction
IU:	International units
IU/dl:	International units per decilitre
IU/kg:	International units per kilogram
n=:	Number
N/A:	Not applicable
OD:	On-demand
PD:	Pharmacodynamics
PEG:	Polyethylene glycol
PK:	Pharmacokinetics
PPX:	Prophylaxis
PTP:	Previously treated patient
PUP:	Previously untreated patient
r:	recombinant
RNAi:	Ribonucleic acid interference
SAE:	Serious adverse events
SD:	Standard deviation
SHL:	Standard half-life
TE:	Thromboembolic events
TMA:	Thrombotic microangiopathy
UK:	United Kingdom
US:	United States
vs:	versus
VWD:	von Willebrand disease
VWF:	von Willebrand factor
wk:	week
WPAI:	Work productivity and activity impairment questionnaire

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

Highlights of this section

In this section we have reports from clinical trials as well as real-world experience on non-replacement therapies.

We saw some preclinical data on the use of MarzAA, a subcutaneous rFVIIa variant, to treat acute bleeds in people with inhibitors and we were given more information regarding the phase III clinical trial for this product. SevenFact ®, a recombinant FVIIa was approved in the US for the treatment of patients with inhibitors.

With regard to patients on Hemlibra®, recommended treatment for acute bleeding in patients with haemophilia A with inhibitors is rFVIIa. There are two interesting studies, one on low dose aPCC and another one in vitro on the use of FIX as alternatives in the potential lack of response to other options. Depending on the results of further clinical studies, these could potentially become alternatives for acute bleeds in inhibitor patients on Hemlibra®. It is important to keep in mind that there is no in vivo evidence to support the use of FIX. Furthermore, it is important to stress that currently the agreed clinical recommendation is to avoid aPCC (unless there is no alternative) in people using Hemlibra® because it can increase their risk of thrombosis. Therefore, the information presented below has to be viewed with caution.

Until recently there were 4 anti-tissue pathway inhibitor (TFPI) molecules in clinical trials. The clinical trial assessing BAY 109388 has stopped due to thrombotic events. We also report on the phase II trial data with regard to the use of concizumab, another anti-TFPI, in patients with inhibitors. The phase III trial of this product has now been paused, after 3 non-fatal thrombotic events.

As a reminder, the abstracts of the EAHAD congress can be accessed online here.

Bypassing agents

Treatment of acute bleeds in patients with haemophilia A and B with inhibitors using MarzAA

In a poster published at the 2019 ASH congress, authors looked at the use of subcutaneous **Marzeptacog alfa (activated) (MarzAA**) for treatment of acute bleeds in people with haemophilia A. To do so, authors used an animal model giving the treatment to mice with haemophilia A and then using a tail clip model to assess efficacy. The experiment showed that MarzAA was efficacious when administered subcutaneously both before and after injury and that this resulted in reduced bleeding in haemophilia A mice similar to non-haemophilia mice and similar to intravenous NovoSeven when dosed one minute after the tail clip. More information was provided at EAHAD 2020 (P128) regarding the phase I of the *MAA-102* study to further determine the pharmacokinetics, pharmacodynamics and safety of a single intravenous dose to treat acute bleeding in haemophilia. The study will enrol at least 8 patients with haemophilia with or without inhibitors to assess 7 dose levels of MarzAA. The investigators in these studies also presented an abstract during the ASH congress in which authors assessed in-vitro thrombin generation of MarzAA, when spiked into haemophilia A plasma containing Hemlibra® at clinically relevant concentrations. Results suggest that, based on these data, MarzAA and NovoSeven are expected to behave similarly when dosed to achieve equipotent plasma concentrations. Additionally, Catalyst Biosciences announced the design of the pivotal phase III *Crimson-1* study will enrol individuals who experience episodic bleeding. Crimson-1 will be an open-label global trial, evaluating the safety and efficacy of subcutaneous MarzAA in the treatment of approximately 230 bleeding episodes in approximately 75 patients, compared with their prior standard of care in a similar number of bleeding episodes. The study will assess the effectiveness of

subcutaneous MarzAA, using up to 3 doses to treat a bleeding episode. The primary endpoint will be the haemostatic efficacy using standard 4-point assessment scale.

Sevenfact approved by the US FDA

The US Food and Drug Administration (FDA) approved in April 2020 **Sevenfact®,** manufactured by the Laboratoire Français du Fractionnement et des Biotechnologies (LFB)**.** This is a recombinant coagulation factor VIIa recombinant, for the treatment and control of bleeding episodes occurring in adults and adolescents (>12 years) with haemophilia A or B with inhibitors. Sevenfact® contains an active ingredient expressed in genetically engineered rabbits, a first for haemophilia treatment.

The safety and efficacy of Sevenfact® were determined using data from a clinical study that evaluated 27 patients with haemophilia A or B with inhibitors, which included the treatment of 465 mild or moderate, and 3 severe bleeding episodes. The proportion of mild or moderate bleeding episodes treated successfully requiring no further treatment for the bleeding episode, no administration of blood products and no increase in pain beyond 12 hours from the initial dose, was approximately 86%. The study also included 3 severe bleeding episodes that were treated successfully with the higher dose. Sevenfact is contraindicated in patients with known allergy or hypersensitivity to rabbits or rabbit proteins.

Bispecific antibodies

Real-world data from the UK on the use of Hemlibra®

During the 2020 EAHAD congress (P075), data were reported on the first year of use of **Hemlibra®** in the UK. All UK non-trial patients with haemophilia A and inhibitors using Hemlibra® between 1/04/2018 and 30/06/2019 were identified. There were 62/202 patients with an active inhibitor (56 severe haemophilia A, 5 moderate and 1 mild) who switched to Hemlibra®. The median age of switchers was 32 (13;48) and non-switchers was 7 (3;18) years old. The median (IQR) historical peak inhibitor titre (BU) for switchers and non-switchers was 19.8 (4-48) and 6.5 (1.2-17.9). The median ABR and AJBR for switchers was 12.5 (3.7;17.2) and 5.8 (1.8;11.4), whilst for non-switchers was 0.8 (0;3.6) and 0 (0;0.9).

A comparison of 21 patients who had ≥ 6 months data, pre- and post- switch was also carried out. This showed a significant reduction in ABR from a median 14.3 to 0 and AJBR reduced from 7.4 to 0. One patient was bleed-free before switching compared with 86% (n=18) bleed free post-switching. One non-fatal adverse event was reported in a patient with established, symptomatic ischemic heart disease, who continued Hemlibra® without further episodes. One patient died from multi-organ failure unrelated to Hemlibra®. There were 5 localized skin reactions reported in 3 patients and there were no reports of loss of efficacy.

Management of breakthrough bleeds in inhibitor patients on Hemlibra®

Mild to moderate bleeding phenotypes are seen in patients on prophylaxis with **Hemlibra®**, thus treatment with factor concentrates will be required to control breakthrough bleeds. In those with inhibitors to haemophilia A, the therapeutic options have been rFVIIa or in the event of a low titre inhibitor FVIII concentrate in some situations. Early in the clinical trials for Hemlibra®, activated Prothrombin Complex Concentrates (aPCC) were contraindicated for the treatment of breakthrough bleeding as there were a number of thrombotic events and fatalities associated with the combination of the two therapies. The mechanism of interaction was that the FIXa present in the aPCC was enhancing the effect of Hemlibra® and accelerating thrombin generation. The recommendation was that, if aPCC was necessary, a low dose would be used not exceeding a defined amount (100 IU/Kg) in a 24-hour period.

In that context, the following 3 studies are interesting. Firstly, in a poster presented at the 2019 ASH congress on the use of aPCC, 3 patients with a history of inhibitors presented with 4 breakthrough bleeds, despite being given prophylaxis with Hemlibra®. Three of the bleeds were the result of trauma and 1 was spontaneous. One of the bleeds was treated with recombinant factor VIII; however, the remaining 3 bleeds were treated with a low dose (15IU/kg) of aPCC as a result of a lack of response to rFVIIa. No patient experienced thrombosis. This case study suggests that low dose aPCC or a continuous infusion of FVIII may be feasible options to treat acute bleeds in patients with inhibitors and on Hemlibra® prophylaxis. This was also investigated in another study at the same congress reporting even lower dose concentrations of aPCC equating doses of ~5 and ~10 IU/kg in order to reach normal thrombin levels.

Then at EAHAD 2020 (P017), investigators presented data on treating bleeds in patients with haemophilia A with inhibitors currently using Hemlibra® by raising levels of FIX. Five patients with inhibitors on prophylaxis with Hemlibra® and 20 healthy controls took part in the study. Therapeutic doses of rFVIIa, aPCC and rFIX were tested. In the results, increments of 25 IU/dL FIX had procoagulant effect similar to what would be obtained after 1 dose of 90 mcg/kg of rFVIIa. Regarding aPCC in ROTEM, increments of FIX levels up to 200 IU/dL were necessary to achieve procoagulant effect similar to a dose of 2.5 IU/kg of aPCC. Thrombin generation was normalized in all patients with increments of 25 IU/dL of FIX. It should be noted that these are in vitro studies and pre-clinical studies are necessary to test the in vivo clinical efficacy and thrombotic risk for concomitant use of FIX and Hemlibra®.

Summary of adverse events with Hemlibra®

During the 2020 EAHAD congress data (P131) was presented on thromboembolic (TE) or thrombotic microangiopathy (TMA) events in people taking **Hemlibra®.** Data on more than 5,200 people having received Hemlibra® between November 2017 and September 2019 were reviewed. Among those with congenital haemophilia A, there were 8 TE events in 7 people and 4 TMA events in 4 people. All but 1 TE event occurred in people with FVIII inhibitors. Overall 2/8 TE events were reported in people receiving concomitant aPCC; of the remaining 6 TEs, 4 were arterial events associated with cardiovascular risk factors, and 2 were venous events associated with venous thromboembolism risk factors. All TMA events were associated with concomitant aPCC use on average 100 IU/kg/24hrs for 24 hours or more. Among all events, all TEs and TMAs were reported as resolved/resolving; none was contemporaneous with fatalities beyond 1 due to rectal haemorrhage reported in the *HAVEN 1* trial. *This abstract was presented by representatives from Genentech and Hoffman La Roche.*

Pre-clinical development of novel bispecific antibodies

There are also 3 new bi-specific antibodies being tested, **Mim8, NXT007** and **KY1049**. Please see Haemophilia A non-replacement section for a short description or click the attached links.

Rebalancing Agents

Please also look at the Haemophilia A section for further information on these products.

Antithrombin

Anti-tissue factor pathway inhibitor antibodies (TFPI)

Concizumab

At ASH 2019, results of the *explorer 4* phase II trial were presented on **concizumab**. This trial tested the use of concizumab, an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development for the subcutaneous treatment of haemophilia patients with inhibitors. Twenty-six patients were randomized to concizumab (9 HAwI and 8 HBwI) prophylaxis or rFVIIa (7 HAwI and 2 HBwI) on-demand treatment. Twenty-five patients completed the main 24-week part of the trial. The

estimated ABR at the last dose level for concizumab prophylaxis was 4.5 and for rFVIIa on demand 20.4. There was a 78%, 88% and 79% reduction in all treated bleeds, spontaneous and joint bleeds, respectively with concizumab prophylaxis compared to on-demand treatment. Concizumab concentration varied considerably between patients on the same dose level. No deaths, thromboembolic events or AEs-related withdrawals occurred. No safety concerns with concomitant use of concizumab and rFVIIa were identified. Three patients had positive (very-low to medium-titer) anti-drug antibody tests but with no apparent clinical effect. Elevated D-dimers were observed across all concizumab dose levels. In addition improvements on quality of life for patients was demonstrated using the SF-36 tool in other reports from this study.

Data was also presented at the ASH congress, on the investigation of the in vitro effect of rFVIIa and aPCC on haemophilia A plasma containing concizumab. This was done to investigate treatment for breakthrough bleeds in haemophilia A inhibitor patients while on concizumab prophylaxis. Addition of rFVIIa or aPCC to haemophilia A plasma with or without inhibitors increased peak thrombin generation both in the absence and presence of concizumab. The effect of concizumab and rFVIIa or aPCC was mainly additive.

A poster at the 2020 EAHAD congress (P196) described a meta-analysis of the phase II clinical data evaluating pharmacokinetics dosing regimen of a loading dose of 1 mg/kg followed by a daily prophylactic dose of 0.25 mg/kg in phase III of *explorer 7* and *explorer 8*.

Subsequently in March 2020, Novo Nordisk indicated that it had paused concizumab treatment in *explorer 5,7 and 8* clinical trials. This means that the trial has temporarily stopped recruitment and dosing around the world. This decision was based on 3 patients experiencing non-fatal thrombotic events in phase III studies. These side effects were not observed in the phase II trials and hence phase III trials could commence. The company are currently reviewing the data and in discussions with regulators.

Clinical studies with BAY 1093884 stopped due to thrombotic events

In another study **BAY 1093884**, another anti-TFPI for non-replacement prophylaxis treatment for patients with haemophilia A or B with or without inhibitors, was also stopped. A phase II study was initiated in July 2018 with a multiple dose, dose-escalating study designed to evaluate the safety of BAY 1093884 in patients with haemophilia A or B with or without inhibitors in 3 dose cohorts (100, 225 and 400 mg). Unfortunately, the study was stopped prematurely after 3 serious adverse thrombotic events (2 at 225 mg dose and 1 at 400 mg dose) - all study-drug related. All occurred in the absence of concomitant use of replacement factors or bypassing agents. An initial evaluation of the pharmacokinetic/pharmacodynamic (PK/PD) data showed that none of the patients who experienced thrombosis had higher levels of BAY 1093884 following subcutaneous administration, or a stronger degree of TFPI inhibition, than patients who did not experience thrombotic events. This absence of specific laboratory findings or any differentiating characteristics in those patients raises concerns about the predictability of thrombosis during the treatment with BAY 1093884. These findings were reported in a poster (P099) during the 2020 EAHAD congress.

OTHER NEWS

Development of diagnostic tool to monitor coagulation status at home

Takeda and Enzyre have announced a collaboration to develop a diagnostic tool that will enable patients with haemophilia to track their coagulation status at home. The idea is that the data collected at home would be immediately transferred to the patient's treating physicians via an app and that this would further facilitate personalized care.

REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	**VWD**	Veyvondi / Vonvendi	rFVIII (vonicog alfa)	Takeda	**Licensed**
Replacement VWF plasma-derived	**VWD Haemophilia A**	Voncento	human coagulation factor VIII / human von willebrand factor	CSL Behring	
Replacement FVIII	**Haemophilia A**	Adynovi / Adynovate / BAX855 / TAK-660 / SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	**Licensed**
		Afstyla / CSL627	rVIII-Single Chain	CSL Behring	
		Elocta / Eloctate	rFVIIIFc (efmoroctocog alfa)	Sobi	
		Esperoct / N8-GP / NNC 0129-0000-1003	rFVIII (turoctocog alfa pegol)	Novo Nordisk	
		Jivi / BAY 94-9027	rFVIII (Damoctocog alfa pegol)	Bayer	
		Kovaltry / BAY 81-8937	unmodified full-length rFVIII (octocog alfa)	Bayer	
		Nuwiq	human-cell-line-recombinant-human-FVIII (simoctocog alfa / human-cl-rhFVIII)	Octapharma	

		BIVV001	rFVIIIFc-VWFD'D3-XTEN	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Alprolix	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**
		Idelvion	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	
		Refixia / Rebinyn	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	
		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 with inhibitors**	Sevenfact	Recombinant FVIIa- jncw	LFB	**Licensed in the US**
	Haemophilia A or B with or without inhibitors	Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**

NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Non-replacement therapy **Bispecific antibody**	**Haemophilia A with or without inhibitors**	Hemlibra / emicizumab / ACE-910	Bispecific antibody	Roche	**Licensed**
	Haemophilia A	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**
		KY1049	Bispecific antibody	Kymab	**Pre-clinical studies**
		NXT007	Bispecific antibody	Chugai	
Non-replacement therapy **Anti-TFPI**	**Haemophilia A or B with or without inhibitors**	Concizumab	Anti-TFPI	Novo Nordisk	**Phase 3** **trial paused**
		BAY 1093884		Bayer	**Phase 2** **Trial terminated due to thrombosis**
		PF-06741086 Marstacimab		Pfizer	**Phase 3**
		MG1113		Green Cross	**Phase 1**
Non-replacement therapy	**Haemophilia A or B with or**	Fitusiran	Antithrombin Small interfering (si)RNA	Genzyme, a Sanofi Company	**Phase 3**

siRNA	**without inhibitors**				
Non-replacement therapy	**Haemophilia A or B with or without inhibitors**	SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1**
GENE THERAPY					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Valoctocogene roxaparvovec/ BMN-270	AAV5-huFVIII-SQ (Valoctocogene roxaparvovec)	BioMarin	**Phase 3**
		SB-525 (giroctocogene fitelparvovec)	Gene therapy using a rAAV2/6 vector	Pfizer (originally Sangamo)	
		BAY-2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
		Spark-8011	AAV-Spark200 encoding BDD-FVIII	Spark	
		TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Phase 1**
		AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	UCL/St. Jude	

		ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Expression Therapeutics	
		AMT-180	Gene therapy using an AAV5-based gene therapy using a FIX variant (FIX-FIAV)	UniQure	**Pre-clinical studies**
		Spark-8016	Modified AAV that carries a bioengineered gene whose protein product can suppress factor VIII inhibitors	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia B**	SPK-9001 PF-06838435 fidanacogene elaparvovec	Padua variant (AAV-Spark100) (fidanacogene elaparvovec)	Pfizer (former collaboration with Spark Therapeutics)	**Phase 3**
		AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	UniQure	
		AMT-060	Gene therapy using AAV5 vector encoding FIX	UniQure	**Phase 1/2**
		SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene	Sangamo	

			into albumin locus		
		FLT180a	AAV encoding FIX Padua variant	Freeline	
		AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	SJCRH	**Phase 1**
		TAK-748 (formerly SHP648/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Takeda	**Pre-clinical studies**
		CB2679d-GT	Novel chimeric AAV vector	Catalyst Biosciences	
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**	YUVA-GT-F801	autologous HSC/MSC modified with lentivirus encoding FVIII	SGIMI	**Phase 1**
		SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Pre-clinical development**

	Haemophilia B	YUVA-GT-F901	autologous HSC/MSC, modified with lentivirus encoding FIX	SGIMI	**Phase 1**