EHC
european haemophilia consortium

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

2019 Issue One

Inhibitors Only

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FOREWORD

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

Unlike the first edition of this review, which was published in May 2018 and is available on the EHC website, this second review is meant to provide a short overview of advances in novel therapeutic medicinal products that occurred between May and January 2019. Therefore this issue will solely provide quick snapshots of notable advances in existing clinical trials, initiation of novel clinical trials and development of novel molecules/treatments in the area of rare bleeding disorders.

As with the first edition, the purpose of this newsletter is primarily to help educate EHC National Member Organisations (NMOs) and help them to provide their members and caregivers with a general overview and understanding of the rapidly evolving landscape of medicinal product development 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.

The information provided in this newsletter is divided by specific type of disorder for which there is an update to report. This next newsletter will be issued in July 2019.

The information provided in this newsletter was compiled from multiple sources, including presentations at recent scientific meetings (e.g. EHC New Technologies workshop, the Annual Meeting of the American Society of Hematology), websites (e.g. www.clinicaltrials.gov) and by writing directly to pharmaceutical companies. It was then redrafted and presented in easy-to-understand language. For this we give special thanks and recognition to Mr Declan Noone and Laura Savini.

The EHC is also grateful to the 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) member
- Asst Prof Brian O'Mahony, EHC President
- Mr David Page, EHC volunteer
- Prof Flora Peyvandi, EHC Medical Advisory Group (MAG) member
- Dr Geneviève Piétu, EHC volunteer
- Dr Uwe Schlenkrich, EHC volunteer

The EHC greatly 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.

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

Sincere regards,

Brian O'Mahony
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

ABR:	Annualised bleeding rate
AIR:	Annualised infusion rate
APC:	Activated protein C
ASH:	American Society of Hematology
AT:	Antithrombin
BPA:	Bypassing agents
EHL:	Extended half-life
EU:	European Union
F:	Factor
FDA:	Food and Drug Administration
ITI:	Immune tolerance induction
IV:	Intravenous
LFT:	Liver function test
NEMJ:	New England Journal of Medicine
SAE:	Serious adverse events
SHL:	Standard half-life
SQ:	Subcutaneous
UK:	United Kingdom
US:	United States
vg/kg:	vector genomes per kilogram
VWF:	Von Willebrand Factor
wk:	week

AN UPDATE ON NOVEL THERAPIES FOR INHIBITOR TREATMENT

Extended half-life (EHL)

An update on MarzAA

Catalyst Bio presented data on its trial of **Marzeptacog alfa (activated) (MarzAA)**.

In a daily **SQ FVIIa** dosing, nine patients have been enrolled with median ABR 16.25. Median SQ bioavailability was 22% and a SQ half-life of 13.1 hours compared to 3.9 hours as IV infusion. There was a fatal hemorrhagic stroke that was determined not to be related to the study drug. The patient had untreated hypertension.

Clinical trial for rFVIIa-FP is terminated

A clinical trial from *CSL Behring* for **rFVIIa-FP has been terminated.**

Non-replacement therapies

Fitusiran

Please see the 'Fitusiran' section in haemophilia A for details with the only modification being, the **phase III trial for those with haemophilia A and B with inhibitors is ATLAS-INH (NCT03417102).**

Hemlibra® (emicizumab)

An update on the HAVEN 2 study

In **updated results** from the **HAVEN 2** (*Roche*) presented at **ASH 2018**, 77% of children with inhibitors treated once weekly (n=65) experienced zero treated bleeds. Once-weekly treatment showed a 99% reduction in treated bleeds compared to prior treatment with bypassing agents (BPAs) as prophylaxis (n=15) or on-demand (n=3) in a prospective intra-patient comparison.

The new data also showed that 90% of children with inhibitors receiving treatment every two weeks (n=10) and 60% of children receiving every four weeks (n=10) experienced zero treated bleeds, demonstrating clinically meaningful bleed control at both dosing schedules.

Gene therapy

Clinical trial to start for gene therapy in people with haemophilia A and inhibitors

Spark has received FDA clearance for **SPK-8016 (NCT03734588)**, a novel, internally developed **AAV gene therapy** candidate aimed at treating patients with **haemophilia A inhibitors** with gene therapy. Data available from animal studies suggest that gene therapy might induce immune tolerance in patients with inhibitors.

Pre-clinical developments of AMT-180 for gene therapy in haemophilia A with and without inhibitors

See section on gene therapy in haemophilia A.

GENE THERAPY COMMENT

With gene therapy for haemophilia on the cusp of entering clinical practice and clinical trials reporting increases in FVIII or FIX activity to almost normal levels, reduced bleed frequency, and a reduced need for FVIII or FIX replacement with a positive and generally manageable safety profile of AAV-mediated vectors, **patients now need to consider a world after the gene transfer**. *Does the individual consider their haemophilia to be 'cured?'* **This creates the need to manage expectations**, particularly regarding

activity levels and bleed risk in the immediate post-treatment period. Despite patients effectively now having a mild phenotype, these individuals may retain a legacy of increased bleed risk and joint damage from their years with severe haemophilia and will **need different clinical management compared to a more typical individual with mild haemophilia**. These are **conversations that need to be addressed** in the near term such as:

- **How a bleed risk is likely to change** (e.g. there may still be some risk of bleeding particularly traumatic bleeds);
- Contacts to discuss **potential positive and challenging emotional issues** resulting from changes in usual haemophilia management;
- Any precautionary requirements to **avoid vertical or environmental transmission** (e.g. use of appropriate barrier contraception during sex until vector has cleared).
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NOTEWORTHY NEWS

Development of APC inhibitor

Activated protein C (APC) breaks down the complex that produces thrombin by inactivating factor Va. Defects in this mechanism (e.g. FV Leiden) are associated with thrombosis but result in less severe bleeding when co-inherited with haemophilia. Selective inhibition of APC might therefore be effective for the treatment of haemophilia. *Apcintex* has developed an **APC inhibitor** but currently does not have a clinical trial, although it could be one to watch for a number of conditions including rare bleeding disorders.

IDO 8 granted orphan drug designation in the EU and US

The IDO 8 from *Idogen* program is aimed at developing a tolerogenic cell therapy for patients with inhibitors, which would be a **cell therapy alternative to immune tolerance induction (ITI)**. Idogen has been granted orphan drug designation in the EU and US.

Developments in cell therapy for haemophilia

HemAcure is an innovative idea that **isolates cells from blood of the haemophilia A patient and performs a genetic (FVIII) correction of those cells**. The corrected cells are expanded, meaning grown in a laboratory, and if enough cells are available to produce sufficient FVIII, corrected cells are transplanted back into the patient in a medical device designed for therapeutic cells (**Cell Pouch™**). The cells in this kind of cell bag or artificial organ are connected with the bloodstream of the patient and that allows a continuous release of FVIII into the patient's blood with the aim of maintaining steady state factor levels. This is in very early development.

Sigilon Therapeutics is also developing a similar strategy with their **SIG-003 program**.

OTHER NEWS

Takeda to take over Shire

Takeda, the Japanese pharmaceutical company, won EU anti-trust approval for its bid for Shire and following the agreement of both sets of shareholders is taking over Shire.