
Article:
Peyvandi, F., Garagiola, I., Boscarino, M. et al. (3 more authors) (2019) Real-life experience in switching to new extended half-life products at European haemophilia centres. Haemophilia, 25 (6). pp. 946-952. ISSN 1351-8216

https://doi.org/10.1111/hae.13834

REAL-LIFE EXPERIENCE IN SWITCHING TO NEW EXTENDED HALF-LIFE PRODUCTS AT EUROPEAN HAEMOPHILIA CENTERS

Flora Peyvandi,[1,2] Isabella Garagiola,[1] Marco Boscarino,[1] Aislin Ryan,[3] Cedric Hermans,[4] Mike Makris[5,6]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Milan, Italy
[2]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy
[3]European Association for Hemophilia and Allied Disorders, Brussels, Belgium
[4]Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[5]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield
[6]Sheffield Haemophilia and Thrombosis Centre, Sheffield, UK

Flora Peyvandi: http://orcid.org/0000-0001-7423-9864
Isabella Garagiola: https://orcid.org/0000-0002-0137-6910
Cedric Hermans: https://orcid.org/0000-0001-5429-8437
Mike Makris: https://orcid.org/0000-0001-7622-7939

Corresponding author: Flora Peyvandi, MD, PhD
Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9, 20122, Milan, Italy
Fax: +39-02-54100125; email: flora.peyvandi@unimi.it

Total Words: 2547

Total Reference: 37

Abstract

The concept of replacement therapy in haemophilia is changing significantly thanks to the switch from standard products to extended half-life products. These novel drugs are showing beneficial effects overcoming current prophylaxis limitations by reducing the infusion frequency, maintaining a higher trough level to ensure a lower risk of bleeding, and making treatment significantly less distressing to patients by improving the quality of life. Real-life data on the efficacy of novel drugs and their impact on routine management of haemophilia A and B patients is still limited. This manuscript reports the results of a European survey conducted by the European Association for Haemophilia and Allied Disorders (EAHAD) at the beginning of 2018 on the clinical management of patients using extended half-life recombinant FVIII and FIX fusion products, since at the time of the survey none of the PEGylated products were available yet. We report data on the efficacy of these novel drugs by 33 European haemophilia centers that have already switched to extended half-life fusion products, showing a significant reduction in the number of infusions and a satisfactory trough levels in the clinical care of haemophilia patients, with a greater impact for haemophilia B.

INTRODUCTION

The clinical picture of haemophilia is characterized by bleeding episodes that occur either spontaneously, in the most severe cases, or as a result of trauma. Repeated spontaneous bleeding episodes mainly affect muscles and joints and lead to chronic arthropathy, with loss of joint movement and fixed flexion deformity (1,2). Prophylaxis with standard FVIII and FIX products is effective at preventing joint damage and decreasing the frequency of hemorrhagic events, as demonstrated in young boys with severe haemophilia (3), but does not assure a complete protection from bleeding with a maximum trough level of 1-2%. However, prophylaxis protocols with these products require recurrent venipuncture (2-3 times per week), and this is one of the main reasons why patients, particularly children and adolescents, decline or discontinue treatment.

Extending the half-life of recombinant products is thought to ease patient management by reducing dosage frequency and prolonging protection from bleeding, which could improve compliance and make this therapy less distressing to the patient (4). Over the last ten years, recombinant factor (F)VIII products for haemophilia A and FIX products for haemophilia B have been remodeled to prolong their half-lives by chemical modification using polyethylene glycol (PEG) polymers and fusion to the fragment crystallizable (Fc) region of an IgG_1 or, alternatively, to human albumin (5-7). The half-lives of the new EHL recombinant FVIII products are approximately 1.5- to 1.6-fold longer compared with standard products (8-10) reducing the frequency of infusions by 30%-35% with a prophylaxis regimen of twice weekly using recombinant FVIII fused to Fc or once every five or seven days using PEGylated concentrates (8-10). These prophylaxis schemes maintain a higher trough FVIII level than standard products: ~3 IU/dL (3%) (11).

EHL recombinant FIX products with a 3-6 fold half-life extension of compared with standard products have certainly simplified the prophylactic regimen of haemophilia B patients, who receive infusions once every 7-14 days in the prophylactic regimen while maintaining FIX trough levels above 5-10% (8-10). Moreover, an ongoing clinical trial with recombinant FIX albumin fusion is investigating whether the dosing interval could be extended to 21 days (clinicaltrials.gov: NCT02053792) (12). Clinical trial outcomes have shown for both EHL recombinant FVIII and FIX drugs that prophylaxis regimens are associated with very low annualized bleeding rates (ABRs) compared to on-demand treatment (11,13-16). These results make such therapies significantly less distressing to the patient (particularly in the case of FIX) and are likely to improve their quality of life (17,18).

EHL products have been licensed at different times in the USA and Europe. In the USA, EHL products were available much earlier than in Europe due to the differences between US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulations for authorizing new products (19). At the beginning of 2018, EHL products available in Europe were limited to recombinant FVIII and FIX fusion products. Real-life evidences have greater value than clinical trials as they provide more accurate responses to questions about patient health and the safety and effectiveness of medical products. Data on the real-life effectiveness of EHL products is still limited and has been reported mainly at international meetings and in a few published reports (20-29).

In this paper, we report the preliminary data on real-life experiences at European haemophilia treatment centers (HTCs), according to a survey administered by the European Association for Haemophilia and Allied Disorders (EAHAD) on the adoption and clinical management of patients using available novel EHL FVIII and FIX products.

The survey was conducted at the beginning of 2018, when a limited number of new EHL products were available in European countries.

MATERIALS AND METHODS

We administered a survey to determine the efficacy of EHL products after they became available in several European countries. At the time of the survey (January 2018), a limited number of EHL products were available: recombinant FVIII and FIX fused to Fc (rFVIII-Fc and rFIX-Fc) and recombinant FIX fused to albumin (rFIX-FP). As for PEGylated products, PEGylated FVIII (BAY94-9027) was not yet approved by the regulatory agency in Europe (EMA), and PEGylated FVIII (BAX855) was approved the same month as our survey (January 2018) but was not yet available at European HTCs. A decision on glycoPEGylated products (N8-GP) was still pending, and recombinant FIX glycoPEGylated (N9-GP) had been licensed in 2017 but was not yet marketed during the survey.

Our unbiased approach to data collection provides a snapshot of the real European experience, and could be used as a baseline from which to compare results over time.

The questionnaire was sent by the EAHAD, in January 2018, to 48 certified European HTCs belonging to the European Haemophilia Network (EUHANET) (https://www.euhass.org/aspxpages/certcentres.aspx).

Each HTCs was asked how long time their center had been using each of the EHL products, what type of EHL product was available at their center, the percentage of haemophilia A and B patients who had switched to EHL products, and the beneficial effects of EHL products in terms of number of infusions, achieved trough level, and percent reduction in bleeding events.

Ethical approval was not required for this study, as the data was collected anonymously and not individually. Our questionnaire did not request specific data for individual patients but general information about the efficacy observed by the HTCs after switching their patients to EHL products.

RESULTS

Thirty-three European HTCs out of 48 submitted a completed questionnaire to EAHAD.

The recombinant FVIII fusion product (rFVIII-Fc) was the EHL drug used routinely for haemophilia A at 76% of the responding centers (25/33). In detail, 55% (18/33) had been regularly using the rFVIII-Fc product for more than a year, 18% (6/33) had experience with this product for three to seven months and only 3% (1/33) had been using it for less than three months. The remaining 24% (8/33) had not yet used it in clinical care (Figure 1). Of these, six European HTCs (Portugal, Czech Republic, Serbia, Bosnia Herzegovina and two centers in Turkey) reported that the new rFVIII-Fc was not available yet, while at the remaining two HTCs, one in Bulgaria and one in France, the product was available but not being used by the physicians.

As for EHL recombinant FIX concentrates, 64% of the responding haemophilia centers (21/33) were regularly using these new drugs. Fourteen centers had experience with both rFIX-Fc and rFIX-FP products, while four used only the rFIX-Fc product and three used only the rFIX-FP. Forty percent (13/33) of the centers had been using the EHL drugs regularly for more than a year, 21% (7/33) for three to seven months, and 3% (1/33) for less than three months. Thirty-six percent (12/33) had not yet used EHL recombinant FIX fusion products for the clinical management of haemophilia B (Figure 1). Of these, at five European HTCs (Portugal, Serbia, Bosnia Herzegovina, and two centers in Turkey), the new EHL recombinant FIX products were not commercially available, while at HTCs in Greece, Finland, Spain (Madrid), UK (London), and France (Paris), the products were available but the centers had not yet switched their patients to the EHL products.

Efficacy data on EHL drug for haemophilia A (rFVIII-Fc)

Twenty-five out of 33 HTCs submitted a reply on the efficacy of the EHL recombinant FVIII fusion product and about 72% of these centers (18/25) had switched less than 10% of their haemophilia A patients from standard products to rFVIII-Fc drug. Two of them (8%) had switched 60-80% of their patients, and none had switched more than 80% (Figure 2).

The positive effects of EHL rFVIII-Fc were evaluated considering the reduction in infusions, trough FVIII level and decrease in bleeding events.

Sixty-six percent of the responding HTCs (15/23) reported a 30% or greater reduction in the number of infusions (Figure 3). The number of infusions decreased by 10% for 17% of the HTCs (4/23), while another 17% reported a decrease of 20%.

Regarding trough level, 33% of the HTCs (7/21) achieved a trough FVIII level of 1-3% and 67% (14/21) achieved a trough FVIII level of 3-5%, while none observed a trough level of more than 5% (Figure 3).

In terms of bleeding events, most centers (57%; 12/21) observed a decrease of less than 20%, 28% (6/21) reported a reduction of the bleeds of 20-50%, while only 5% (1/21) observed a decrease of 50-99%. Ten percent of the responding HTCs (2/21) reported a 100% decrease in bleeds (Figure 3).

Efficacy data on EHL drugs for haemophilia B (rFIX-Fc and rFIX-FP)

Forty-three percent of responding HTCs (9/21) using EHL drugs for haemophilia B had switched 10-40% of their haemophilia B patients from standard therapy to the EHL recombinant FIX concentrates. Nineteen percent (4/21) had switched the majority of their patients (80-100%) to EHL products (Figure 2).

All responding HTCs revealed a reduction in infusions of more than 30% (Figure 3).

The clinical use of EHL recombinant FIX products led to an FIX trough level of at least 5-10% in 67% of centers (14/21), while 19% (4/21) achieved an FIX trough level of 3-5% (Figure 3). Only three centers (14%) observed a low trough level of 1-3%.

A 100% decrease in bleeding events was reported in almost one third of the responding centers (5/18), while 33% (6/18) observed a decrease of 20-50% and 39% of the centers (7/18) revealed a decrease in bleeding episodes of less than 20% (Figure 3).

DISCUSSION

The concept of haemophilia replacement therapy is changing thanks to the introduction and licensing of novel EHL recombinant FVIII and FIX products in the European market. A well designed study to assess the real efficacy and safety of these novel EHL drugs is needed to allow proper use in the routine clinical care of bleeding events, prophylaxis, and surgical management of patients with haemophilia A and B, and to work toward the possible revision of prophylactic treatment schedules.

In this report, we provide very preliminary data on the efficacy of a few novel EHL drugs (rFVIII-Fc, rFIX-Fc and rFIX-FP) that were commercially available in Europe at the time of the EAHAD survey, with 33 responding European HTCs. The survey suffers from a few limitations.

First, our data does not include PEGylated FVIII and FIX products, which were not yet available in Europe at the time of the survey so results are limited to the three EHL fusion products mentioned above. Additionally, we do not report any data on safety assessment, which is not completely known and requires a proper long-term surveillance using a consensus minimal dataset collection tool as recommended by the ISTH Scientific and Standardization Subcommittee (SSC) working group (30). The onset of inhibitors is an important safety issue relating to newly licensed EHL drugs, to be addressed when data from the ongoing previously untreated patients (PUPs) studies is available. Another significant safety issue is the potential risk of PEG accumulation in haemophilia associated with long-term and chronic administration (31,32). Long-term surveillance is required to understand the effect of longstanding PEG exposure. The currently available information obtained from the approved PEGylated products does not indicate any specific human toxicity, as these products are not for life-long use as is the case for haemophilia.

The outcomes reported by the 33 responding HTCs to the EAHAD survey showed a beneficial effect of EHL FVIII products in reducing the number of infusions, by ≥30% in 66% of the responding HTCs using the new drugs; in trough levels, where a value of 3-5% was reached by 67% of centers; and in decreasing bleeding episodes by ≤50% at 86% (18/21) of responding HTCs. The number of patients switched to EHL drugs was still low, with the majority of HCTs (72%) having switched less than 10% of their haemophilia A patients. Recent real-world experiences have also confirmed our survey data that treatment with the new EHL recombinant FVIII products reduces the number of infusions by 30-40% with a substantially lower ABR in patients receiving prophylaxis compared to on-demand treatment (20-29,33,34).

Our survey on EHL recombinant FIX showed a significant reduction in infusion frequency at 100% of the centers, with 67% achieving a trough FIX level of at least 5 to10%. Forty-three percent of HTCs have switched 10-40% of their patients from standard therapy to EHL drugs. Recent publications on real-world outcomes have shown a 50-60% reduction in infusions, confirming our preliminary analysis at European HTCs (21,22,28,29,33-37). Therefore, this very preliminary data obtained by survey reflects beneficial efficacy effects in both haemophilia A and haemophilia B using EHL fusion products, with especially pronounced results in haemophilia B. These novel products have almost made it possible to improve severe haemophilia A patients to moderate phenotype by following an infusion schedule of two times a week or every five days, and to alter the clinical picture of haemophilia B patients from severe to mild phenotype through one single infusion every 7 or 10 days. It would be worthwhile to conduct another survey of the same European HTCs in the near future, to monitor the usage rate, efficacy, and also the safety of these novel products.

These new drugs are also becoming more widely used in clinical practice in the United States, such that the proportion of patients switched to prophylaxis with EHL recombinant FVIII and FIX has increased substantially since FDA approval. Recent data by Aledort et al (33) showed that the number of haemophilia A patients switched to EHL recombinant FVIII increased from 13% in 2014 to 21% in 2018, and for the haemophilia B patients, the number rose from 25% in 2014 to 57% in 2018 (33). Recent data presented during the ASH 2018 annual meeting by the American Thrombosis and Hemostasis Network (ATHN) reported that 21% of patients with moderate or severe haemophilia A and 42% of patients with moderate or severe haemophilia B have received prophylaxis using an EHL product (34). The shift to EHL drugs is transforming haemophilia care by achieving improved bleeding control and higher trough levels, thereby improving long-term joint protection.

More real-life experience is necessary to provide insights into how physicians and patients make treatment choices and into the dosing regimens used in the clinical setting. Evaluating the safety of these new drugs is of the utmost importance and should be monitored through careful, long-term observation of any unexpected effects occurring after marketing authorization. Recently, following recommendations published by the ISTH Scientific and Standardization Subcommittee (SSC) on Factor VIII, Factor IX and Rare Coagulation Disorders for post-registration surveillance of new drugs in haemophilia (30), a new pharmacovigilance system for EHL products has been developed in the form of a mobile phone app (mAPPHemo) that patients and their physicians can use to record treatments and any complications that may arise. This tool, or any other national or international surveillance system such as the pharmacovigilance program of EUHASS, will be helpful in identifying all known and unknown side effects of these newly licensed products. Recently, the EMA also reported the importance of long-term surveillance.

In conclusion, the arrival of novel EHL drugs and their widespread adoption have changed the clinical management of haemophilia A by reducing the number of infusions and achieving higher trough levels and better protection. These effects appear to be even more significant for haemophilia B patients. The safety and efficacy of new concentrates has to be monitored continuously in order to update haemophilia management and develop evidence-based guidelines for the correct use of new EHL drugs in the routine clinical care of haemophilia.

Acknowledgements

We thank all following physicians for participating in this EAHAD survey study:
Amparo Santamaría Ortiz, Haemostasis and Thrombosis Unit, University Hospital Vall d'Hebron, Barcelona, Spain; Andrew Will, Royal Manchester Children's Hospital, Manchester, United Kingdom; Anne Wareing, St George's Haemophilia Centre, London, United Kingdom; Beatrice Nolan, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland; Bulent Zulfikar, Ege Hemophilia Center, Ege University Children's Hospital , Izmir, Turkey; Campbell Tait, Haemophilia and Thrombosis Centre (Adults), Glasgow Royal Infirmary, Glasgow, United Kingdom; Chiara Ambaglio, Centro Emofilia e Coagulopatie Congenite, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Claudio Molinari, Haemostasis and Thrombosis Unit, Gianna Gaslini Children's Institute, Genoa, Italy; Cristina Santoro, Centro Emofilia, Diagnosi Speciale e Terapia della Malattie dell'Emostasi e della Trombosi, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy, Danijela Mikovic, Blood Transfusion Institute of Serbia, Belgrade, Serbia; Elina Armstrong, Coagulation Disorders Centre, Helsinki University Central Hospital, Helsinki, Finland; Ezio Zanon, Hemophilia Centre of Padova, Padua, Italy; Helen Platokouki, Haemophilia Centre and Haemostasis Unit, Aghia Sophia Children's Hospital, Athens, Greece; Herman Cedric, Cliniques Universitaires Saint-Luc, Brussels, Belgium; Ingrid Pabinger-Fasching, Haemophilia Centre Vienna, Vienna General Hospital, Vienna, Austria; Jan Blatny, University Hospital Brno, Brno, Czech Republic; Jenny Goudemand, Unité d'Hémostase, Clinique du CHRU de Lille, Lille, France; Johanna A. Kremer Hovinga, Haemphilia Haemophilia Comprehensive Care Centre, Bern University Hospital, Bern, Switzerland; Kaan Kavakli, Istanbul University Haemophilia Centre, Istanbul; Turkey; Karin Kurnik, Paediatric Haemophilia Centre Munich, Munich, Germany; Karina Mejer, Haemophilia Treatment Centre Groningen, University Medical Centre Groningen, Groningen, The Netherlands; Kathelijne Peerlinck, Haemophilia Center, UZ Leuven, Leuven, Belgium; M. Joäo Diniz, Haemophilia Centre, Hospital de S. Jose, Lisbon, Portugal; Maria Elisa Mancuso and Elena Santagostino, Angelo Bianchi Bonomi Hemophilia and Thrombosis Unit, Milan, Italy; Mike Makris, Sheffield Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, United Kingdom; Niamh O'Connell, The National Coagulation Centre, St James's Hospital, Dublin, Ireland; Olga Katsarou, National Reference Centre for Congenital Bleeding Disorders, Laiko General Hospital, Athens, Greece; Pierre Fontana, Centre for Haemophilia and Allied Disorders, University Hospitals of Geneva, Switzerland; Predojevic Jelica, Haemophilia Centre Banja Luka, University Clinical Centre of the Republic of Srpska, Bosnia and Herzegovina; Robert Klamroth, Vivantes Haemophilia Treatment Centre Berlin Friedrichshain, Berlin, Germany; Thierry Lambert, Bicêtre Haemophilia Treatment Centre, Hôpital Bicêtre, Paris,

France; Toshko Jelev Lissitchkov, Haemophilia Comprehensive Care Centre, National Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria; Victor Jiménez Yuste, Haemostasis Unit, Hospital Universitario La Paz, Madrid, Spain.

Authorship

F.P. and I.G. contributed to the development and writing of the manuscript, M.B. analyzed the data. A.R., C.H. and M.M. revised the manuscript providing critical input and participated in data submission.

Conflict of interest

F.P. has received honoraria for participating as a speaker at satellite symposia organized by Alnylam, Grifols, Kedrion, Roche, Takeda. F.P. reports participation at advisory board of Bioverativ, Roche, Sanofi and Takeda.

I.G., M.B. and A.R. declare no competing financial interests.

C.H. has received honoraria for consultancy/advisory boards from LFB, CSL-Behring, CAF-DCF, Octapharma, Bayer, Shire, Sobi/Biogen, Kedrion, Pfizer.

M.M. has acted as consultant or participated in advisory panels for Bioverativ, CSL Behring, NovoNordisk and Shire. M.M. is also the project leader for EUHASS which receives funding from Bayer, Biotest, BPL, CSL Behring, Grifols, Kedrion, LFB, NovoNordisk, Octapharma, Pfizer, Roche, Shire and Sobi

REFERENCES

1. Mannucci PM, Tuddenham EG. The haemophilias--from royal genes to gene therapy. *N Engl J Med.* 2001;344:1773-1779.
2. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet.* 2016;388:187-197.
3. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med.* 2007;357:535–544.
4. Shapiro A, Chaudhury A, Jain N, Tsao E, Barnowski C, Feng J, Quon D. Real-World Data on the Use of rFIXFc in Subjects With Hemophilia B for Up to 3.7 Years Demonstrates Improved Bleed Control and Adherence With Reduced Treatment Burden. Blood. 2018;132 (Suppl.1):2493
5. Peyvandi F, Garagiola I, Seregni S. Future of coagulation factor replacement therapy. *J Thromb Haemost.* 2013;11 Suppl 1:84-98.
6. Ragni M. New and Emerging Agents for the Treatment of Hemophilia: Focus on Extended Half-Life Recombinant Clotting Proteins. *Drugs.* 2015;75:1587–1600.
7. Peyvandi F, Garagiola I. Treatment of haemophilia in the near future. *Semin Thromb Hemost.* 2015;41:838-848.
8. Powell JS. Longer-acting clotting factor concentrates for hemophilia. J Thromb Haemost. 2015 Jun;13 Suppl 1:S167-75.
9. Peyvandi F, Garagiola I, Biguzzi E. Advances in the treatment of bleeding disorders. J Thromb Haemost. 2016;14:2095-2106.
10. Berntorp E, Andersson NG. Prophylaxis for Hemophilia in the Era of Extended Half-Life Factor VIII/Factor IX Products. Semin Thromb Hemost. 2016;42:518-525.
11. Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, Hanabusa H, Gupta N, Kulkarni R, Fogarty P, Perry D, Shapiro A, Pasi KJ, Apte S, Nestorov I, Jiang H, Li S, Neelakantan S, Cristiano LM, Goyal J, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe haemophilia A. *Blood.* 2014;123: 317-325.
12. Santagostino E, Martinowitz U, Lissitchkov T, Pan-Petesch B, Hanabusa H, Oldenburg J, Boggio L, Negrier C, Pabinger I, von Depka Prondzinski M, Altisent C, Castaman G,

Yamamoto K, Álvarez-Roman MT, Voigt C, Blackman N, Jacobs I; PROLONG-9FP Investigators Study Group. Long acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in haemophilia B: results of a phase 3 trial. *Blood.* 2016;127:1761-1769.

13. Mahdi AJ, Obaji SG, Collins PW. Role of enhanced half-life factor VIII and IX in the treatment of haemophilia. *Br J Haematol.* 2015;169:768–776.

14. Lyseng-Williamson KA. Coagulation Factor IX (Recombinant), Albumin Fusion Protein (Albutrepenonacog Alfa; Idelvion®): A Review of Its Use in Haemophilia B. Drugs. 2017;77:97-106.

15. Oldenburg J, Carcao M, Lentz SR, Mahlangu J, Mancuso ME, Matsushita T, Négrier C, Clausen WHO, Ehrenforth S, Young G. Once-weekly prophylaxis with 40 IU/kg nonacog beta pegol (N9-GP) achieves trough levels of >15% in patients with haemophilia B: Pooled data from the paradigm™ trials. *Haemophilia.* 2018;24:911-920.

16. Carcao M, Lambert T, Leissinger C, Escuriola-Ettingshausen C, Santagostino E, Aledort L; International Prophylaxis Study Group (IPSG). Prophylaxis re-visited: The potential impact of novel factor and non-factor therapies on prophylaxis. *Haemophilia.* 2018;24:845-848.

17. Wyrwich KW, Krishnan S, Auguste P, Poon JL, von Maltzahn R, Yu R, Pierce GF, Mei B, Mahlangu J, von Mackensen S. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Haemophilia. 2016;22:866-872.

18. von Mackensen S, Shah J, Seifert W, Kenet G. Health-related quality of life in paediatric haemophilia B patients treated with rIX-FP. Haemophilia. 2019;25:45-53.

19. Peyvandi F, Rosendaal FR, O'Mahony B, Mannucci PM. Pediatric requirements in Europe stymie help for hemophilia. Nat Med. 2014;20:466.

20. Dunn AL, Ahuja SP, Mullins ES. Real-world experience with use of Antihemophilic Factor (Recombinant), PEGylated for prophylaxis in severe haemophilia A. *Haemophilia.* 2018; 24(3):e84-e92.

21. Keepanasseril A, Stoffman J, Bouskill V, Carcao M, Iorio A, Jackson S; Association of Haemophilia Centre Directors of Canada (AHCDC). Switching to extended half-life products in Canada - preliminary data. *Haemophilia.* 2017 Jul;23(4):e365-e367.

22. Wang C, Young G. Clinical use of recombinant factor VIII Fc and recombinant factor IX Fc in patients with haemophilia A and B. *Haemophilia.* 2018;24:414-419.

23. Tagliaferri A, Quintavalle G, Riccardi F, Matichecchia A, Benegiamo A, Rossi R, Coppola A. Benefits of switch to FVIII-FC: Experience of prophylaxis in eight patients. *Haemophilia.* 2018; 24 Suppl 1;55.
24. Jimenez R, Nuñez R, Jimenez P, Rodriguez-Martorell FJ, Perez-Simon JA. Switch to extended half-life recombinant factor VIII FC in severe haemophilia A patients under prophylaxis. Experience in one centre. *Haemophilia.* 2018; 24 Suppl 1;117.
25. Prunty K, Brady B, Kelly I, Kavanagh M, Ryan C, Nolan B. Real world experience of Elocta in paediatric patients with severe haemophilia A in Ireland. WFH 2018 World Congress; *Haemophilia.* 2018;S5;27.
26. Scott M, Xiang H, PW Collins, Hay CRM. The effect of switching to rFVIIIFc on treatment patterns and annualized bleed rate before and after: A within-patient comparison from the UK National Haemophilia Database. WFH 2018 World Congress; *Haemophilia.* 2018; Issue S5; 91
27. Pouplard C, Sattler L, Ryman A, Eschwege V, De Maistre E, Flaujac C, Szymezak J, Grand F, Repesse Y, Galinat H, Donnard M, Ternisien C, Jeanpierre E. Multicenter Pharmacokinetic Evaluation of rFVIII-Fc (Elocta) in a Real Life and Comparison with Non-Extended Half-Life FVIII Concentrates. *Blood.* 2018;132 (Suppl.1):1196.
28. Chalmers E, Bagot C, Campbell Tait R, Anderson J, Rodgers R, Khan M, Watson H, Craig J, Kerr R, McLaughlin D. Scottish experience introducing extended half-life factor concentrates in Haemophilia A and Haemophilia B patients. WFH 2018 World Congress; *Haemophilia.* 2018;S5;27.
29. Phillott A, Stanley J, Alamelu J. Single centre experience of switching from standard half-life to extended half-life products in patients with severe haemophilia A and B. WFH 2018 World Congress; *Haemophilia.* 2018;S5; 32.
30. Peyvandi F, Makris M, Collins P, Lillicrap D, Pipe SW, Iorio A, Rosendaal FR; Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. Minimal dataset for post-registration surveillance of new drugs in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15:1878-1881.
31. Ivens IA, Achanzar W, Baumann A, Brändli-Baiocco A, Cavagnaro J, Dempster M, Depelchin BO, Rovira AR, Dill-Morton L, Lane JH, Reipert BM, Salcedo T, Schweighardt B, Tsuruda LS, Turecek PL, Sims J. PEGylated Biopharmaceuticals: Current Experience and Considerations for Nonclinical Development. Toxicol Pathol. 2015;43:959-83
32. Turecek PL, Bossard MJ, Schoetens F, Ivens IA. PEGylation of Biopharmaceuticals: A Review of Chemistry and Nonclinical Safety Information of Approved Drugs. J Pharm Sci. 2016;105:460-475.

33. Aledort LM, Jain n, Li N, Krishnan S, Hagberg B, Su j. Changing the Paradigm in Hemophilia Care: Extended Half-Life Products (rFVIIIFc and rFIXFc). *Blood.* 2018;132 (Suppl.1):3514.
34. Malec LM, Witmer CM, Jaffray J, Kouides PA, Haley KM, Sidonio RF, Cheng D, Abshire TC, White GC, Ragni MV. Real World Use of Extended Half-Life Products and the Impact on Bleeding Events and Joint Health in the United States. *Blood.* 2018;132 (Suppl.1):1195.
35. O'Connell N, Lavin M, Byrne M, Dalton N, Ryan K, White B, O'Donnell J, Singleton E. An en-masse switch to extended half life recombinant factor IX replacement therapy in Irish adults with Haemophilia B. WFH 2018 World Congress; *Haemophilia.* 2018; Issue S5; 29
36. Ragni M, Kulkarni R, Pasi KJ, Fischer K, Mahlangu J, Shapiro A, Nolan B, Oldenburg J, Matsushita T, Willemze A, Yuan H, Rudin D. B-YOND Final Results Confirm Established Safety, Sustained Efficacy, and Extended Dosing Interval for Up to 4 Years of Treatment With rFIXFc in Previously Treated Subjects With Severe Hemophilia B. *Blood.* 2018;132 (Suppl.1):1214.
37. Shapiro A, Chaudhury A, Jain N, Tsao E, Barnowski C, Feng J, Quon D. Real-World Data on the Use of rFIXFc in Subjects With Hemophilia B for Up to 3.7 Years Demonstrates Improved Bleed Control and Adherence With Reduced Treatment Burden. *Blood.* 2018;132 (Suppl.1):2493.

FIGURE LEGENDS

Figure 1. Number and percentage of European HTCs by usage time of new EHL products for the treatment of haemophilia A (left) and B (right).

Figure 2. Percentage of haemophilia patients switched from standard products to EHL recombinant FVIII and EHL recombinant FIX drugs.

Figure 3. Efficacy of EHL FVIII and FIX concentrates: reduction of infusions, trough level and reduction of bleeding events.