

Defining extended half-life rFVIII—A critical review of the evidence

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Introduction: Recent haemophilia treatment advances include new recombinant FVIII (rFVIII) products with improved pharmacokinetic (PK) properties that aim to reduce the burden of prophylaxis. These treatments are commonly referred to as extended half-life rFVIII products (EHL rFVIII). There is no uniform definition of what constitutes an EHL rFVIII. Such a definition would help physicians, patients and funders understand the properties of standard and EHL rFVIII and thus provide clarity when selecting an EHL in clinical settings.

Aim: To critically assess the published evidence on new and emerging rFVIII products in order to propose a definition to classify EHL rFVIII.

Methods: We systematically searched PubMed, EMBASE and regulatory authorities (FDA/EMA/Health Canada) websites for publications and regulatory submissions describing prospective crossover PK studies evaluating rFVIII that demonstrate improved PK parameters in adults and adolescents with severe haemophilia A.

Results: Following critical analyses of the published data, we developed a holistic approach to defining rFVIII as EHLs, which requires all of the following: (i) using technology designed to extend rFVIII half-life; (ii) lacking bioequivalence with a standard rFVIII comparator—above the FDA/EMA cut-off of 125% for the 90% confidence intervals for area under the curve ratio; and (iii) having an extended half-life ratio measured in a PK comparator crossover study.

Conclusion: In this systematic review, a pragmatic definition of EHL rFVIII has been proposed that should provide better clarity in clinical discussions surrounding the appropriate use of rFVIII products. At present, only products using PEGylation or Fc fusion half-life extension technology meet the proposed criteria for definition of EHL rFVIII.

KEYWORDS

bioequivalence, extended half-life, haemophilia A, prophylaxis, recombinant factor VIII

1 | INTRODUCTION

Over the last 6 decades, the management and outcomes of severe haemophilia A (FVIII <1% of normal) have greatly progressed with the development and technological advances associated with FVIII

replacement therapy. Primary FVIII prophylaxis has been shown to be an effective approach to minimizing joint damage.¹ However, adherence is often less than optimal because prophylactic regimens with standard rFVIII concentrates are time-consuming and involve frequent venipunctures or use of central venous access for administration of

infusions.² Although there are intra- and interindividual variances, on average, standard rFVIII has a plasma half-life of ~12 hours and requires approximately 3 to 4 infusions per week for effective prophylaxis.³ Lack of adherence to FVIII prophylaxis is a key determinant of increased bleeding.² Therefore, as only a few haemarthroses can have a debilitating impact,⁴ strict adherence to bleed prevention regimens is important for preservation of joint function.²

To address the burden of frequent prophylactic rFVIII infusions, several rFVIII products have been designed to improve their pharmacokinetics (PKs) properties.⁵ Prophylaxis with an extended half-life (EHL) rFVIII replacement therapy with correspondingly longer intervals between doses has the potential to reduce the burden of infusions and/or achieve higher FVIII trough levels.⁶ Recently, many new rFVIII products have entered the market, including some with PK characteristics that have evolved as a result of other enhancements made to the parent compound (such as manufacturing improvements). Regulatory-approved dosing regimens for new rFVIII products do not differentiate standard from EHL. Some products list a dosing frequency range that includes both standard (3+ weekly infusions) and extended dosing (2 weekly infusions).⁷⁻⁹ In the clinical studies on which these dosing recommendations are based, approximately one-third of participants had twice weekly dosing, while the rest had shorter dosing intervals.^{7,9} Ideally, an EHL rFVIII should allow reduced dosing frequency with retention of haemostatic efficacy compared to standard half-life rFVIII *for the majority of patients*. The current literature also does not provide clarity on what constitutes an EHL rFVIII product. Some authors conclude that rFVIII products have enhanced PK properties based on absolute half-lives that are higher than average standard rFVIII, comparing data from different studies.¹⁰⁻¹² However, absolute half-lives should not be compared across studies because different assays, populations

and statistical analysis methods all affect the absolute half-life observed.¹³⁻¹⁵ To keep these variables constant, the International Society on Thrombosis and Haemostasis (ISTH), European Medicines Agency (EMA), and US Food and Drug Administration (FDA) guidance recommend studying a new rFVIII and a similar test product in the same individual.¹⁶⁻¹⁸ These data can be used to calculate a half-life ratio (half-life of study product: half-life of comparator product) for valid comparison of PK parameters across different studies of different rFVIII products.

With several new options available, a better understanding of the potential benefits and limitations of rFVIII products could be gained through clear categorization of currently available EHL FVIII products. Herein, we propose criteria for defining EHL rFVIII products, and then, we apply these parameters to assess which new rFVIII products are EHLs based on the available evidence from well-designed PK studies where a product is sequentially compared to a reference in the same individual.

2 | MATERIALS AND METHODS

This systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline.¹⁹ Search and selection strategies were developed into a protocol and applied by an independent researcher to validate the results.

2.1 | Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed to select for well-designed PK comparator studies (Table 1); these criteria were informed by the ISTH Scientific and Standardization Committee's guidance.

TABLE 1 Inclusion and exclusion criteria¹⁶

Inclusion	Exclusion
Study design	
Comparison with standard FVIII product(s) controls tested within the same individual	Lack of FVIII comparator or comparison between different populations
Washout	No washout
Testing with one-stage or chromogenic assay for both FVIII products	Other assay methodologies
Minimum sample size of 12 and/or sufficiently powered to make a comparison between the study rFVIII and comparator rFVIII	Sample sizes <12 or insufficiently powered
Study results	
Reporting pharmacokinetic results for the study rFVIII and comparator rFVIII, including at least population mean or median for half-life, AUC	Pharmacokinetic results not sufficiently reported
Patients	
Humans	Animals, <i>in vitro</i> studies, modelling/simulation
Haemophilia A	Haemophilia B, VWF disease and other diseases
Severe disease (FVIII ≤1%)	FVIII >1%
No evidence of inhibitors	Evidence of inhibitors
Age >12 years	Age <12 years
Products	
rFVIII products for prophylactic use with claimed altered pharmacokinetic properties	Other anticoagulants (FVII, FIX, VWF, FVIII/VWF), standard rFVIII, plasma-derived FVIII



2.2 | Search strategy and study selection

Searches of 2 electronic databases (MEDLINE (<https://www.ncbi.nlm.nih.gov/pubmed>) and EMBASE (www.embase.com)) were carried out using the following terms: *search 1*: "('extended halflife' OR 'extended half life' OR 'extended half-life') OR ('prolonged halflife' OR 'prolonged half life' OR 'prolonged half-life') AND ('factor VIII' OR FVIII) AND (pharmacokinetics OR pharmacokinetic) AND sequential"; *search 2*: "(factor AND viii OR FVIII) AND pharmacokinetics AND ('cross over' OR crossover OR 'cross-over')"; *search 3*: "(((('extended half life' OR 'extended half-life' OR 'extended halflife OR EHL) OR ('prolonged halflife' OR 'prolonged half life' or 'prolonged half-life')) AND ('factor VIII' OR FVIII)) AND (pharmacokinetics OR pharmacokinetic) AND ('cross-over' OR crossover)"; *search 4*: "(((('extended half life' OR 'extended half-life' OR 'extended halflife' OR EHL) OR ('prolonged halflife' OR 'prolonged half life' or 'prolonged half-life')) AND ('factor VIII' OR FVIII) AND (pharmacokinetics OR pharmacokinetic) AND ('cross-over' OR crossover)"; *search 5*: "((('factor VIII' OR FVIII) AND (pharmacokinetics OR pharmacokinetic) AND (longacting or 'long-acting' or 'long acting'))"; *search 6*: "Nuwiq and pharmacokinetics" (as this product was not returned in the generic searches). Searches included primary papers, published before 31 August 2017. Primary reports of clinical studies (either peer-reviewed

papers or regulatory body documents) were included; review articles, case studies, letters and conference abstracts were excluded.

Searches were also carried out using a simplified combination of search terms ((factor VIII or FVIII) and pharmacokinetics) and manual searching for product names on websites of regulatory agencies for medicines and biological, for example USA (FDA <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>), European (EMA <http://www.ema.europa.eu/>) and Canadian (Health Canada <http://www.hc-sc.gc.ca/index-eng.php> and <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp> for individual product searches). Searches for rFVIII products were informed by the MEDLINE and EMBASE results and employed both generic and brand names (Table 2) as search terms, and reflected the results available as of 31 August 2017.

The relevance of each article or report identified during the search process was assessed by applying the inclusion and exclusion criteria and initially screening titles and abstracts to select publications for more further considerations.

2.3 | Data extraction and analysis

Data were extracted into a standardized electronic format, including study design, subject characteristics and numbers, and key PK data.

TABLE 2 PK studies which fulfilled inclusion criteria

PK studies	rFVIII product	rFVIII design	Modification to extend the half-life
Phase 1 NCT01599819 ^{22,47} Phase 2/3 NCT01736475 PROLONG-ATE ^{22,47a}	BAX 855 (Adynovi/ Adynovate [®])	- Full-length human rFVIII, based on Advate - Produced in CHO cells^{29,48}	Covalent attachment of branched 20 kDa PEG chains to primary amines (primarily lysine and approximately 2 moles PEG per FVIII molecule) ^{29,48,49}
Phase 1/3 NCT01486927 ^{24,25,50}	rFVIII-SingleChain (Afstyla [®])	- Single rFVIII polypeptide chain with a truncated B-domain - Produced in CHO cells^{9,24,25,50}	The stabilised single-chain increases the affinity to VWF ^{24,25}
Phase 1 NCT01184820 ^{21a}	BAY 94-9027	- B-domain deleted rFVIII²¹ - Produced in HKB11 cells (human kidney/B-cell hybrid)⁵¹	60 kDa PEG-conjugated to a single cysteine residue
Phase 1/2a NCT01027377 ^{52,53} Phase 3 NCT01181128 A-LONG ^{23,54,56-58}	rFVIII-Fc (Elocta/ Eloctate [®])	- B-domain deleted rFVIII with modifications to enable Fc fusion - Produced in HEK cells^{54,55}	Covalent attachment to the dimeric Fc domain of human IgG ₁ , enabling binding to the neonatal Fc receptor (FcRn) which protects IgG from degradation ⁵⁴⁻⁵⁶
Phase 1 NCT02483208 ³⁸ Phase 1/3 NCT01029340 Leopold I ^{32,59-61}	BAY 81-8973 (Kovaltry [®])	- Full-length rFVIII based on Kogenate FS - Produced in a genetically engineered BHK cell line which produces human heat shock protein 70^{7,32,33,59}	None
Phase 1 NCT01205724 Pathfinder ^{™37}	N8-GP	- B-domain truncated rFVIII - Produced in CHO cells³⁷	A branched 40 kDa PEG-conjugated to a terminal sialic acid on an O-glycan structure in the truncated B-domain ³⁷
Phase 2 NCT00989196 GENA-01 ^{35,62}	Human-cl rhFVIII (Nuwiq [®])	- B-domain deleted rFVIII - Produced in genetically engineered HEK cells^{35,63}	None

BHK, Baby Hamster Kidney; CHO, Chinese hamster ovary; HEK, human embryonic kidney; PEG, polyethylene glycol; PK, pharmacokinetic; VWF, von Willebrand factor.

^aAdditional data were obtained directly from Shire and Bayer in response to information requests.

Some of the included publications and government documents did not calculate half-life ratios, instead reporting only the absolute half-life in hours for the studied rFVIII and standard comparators. In these cases, a half-life ratio was calculated by dividing the half-life reported for the studied rFVIII product by that reported for the standard rFVIII control.

3 | RESULTS

In the literature screening, a total of 339 potentially relevant references were found, and 31 publications/reports/monographs (Table S1) reporting on 11 studies were ultimately selected for qualitative analysis (some data were included in more than one source). Figure 1 depicts the study selection process. One PK study was subsequently excluded from the final analysis²⁰ because the product, BAY 79-4980, has been discontinued. The PK studies included in the final analysis are provided in Table 2.

3.1 | Rational design: products intended to have extended half-life

Established methods that have been applied to extend the half-life of rFVIII include PEGylation—the chemical addition of a polyethylene glycol (PEG) to rFVIII^{21,22}—and Fc fusion—the covalent binding of rFVIII to the Fc domain of IgG₁.²³ A novel approach to improve rFVIII PK characteristics is the formation of a “single-chain” by covalent binding of rFVIII heavy and light chains.^{5,24,25}

With more than 25 years of accumulated experience, PEGylation is a well-established technology for prolonging the half-life of proteins.²⁶ The technology has been used in twelve approved medicinal products since the 1990s and in more in development.^{27,28} In the case of rFVIII, 3 products (BAX 855, BAY 94-9027 and N8-GP) employ PEGylation, albeit with different size PEG molecules (Table 2), to extend half-life by disrupting interactions with the low-density lipoprotein receptor-related protein (LRP) 1. This protein is responsible for the physiological clearance of FVIII; interfering with this interaction may lead to reduced hepatic clearance of rFVIII.^{21,29}

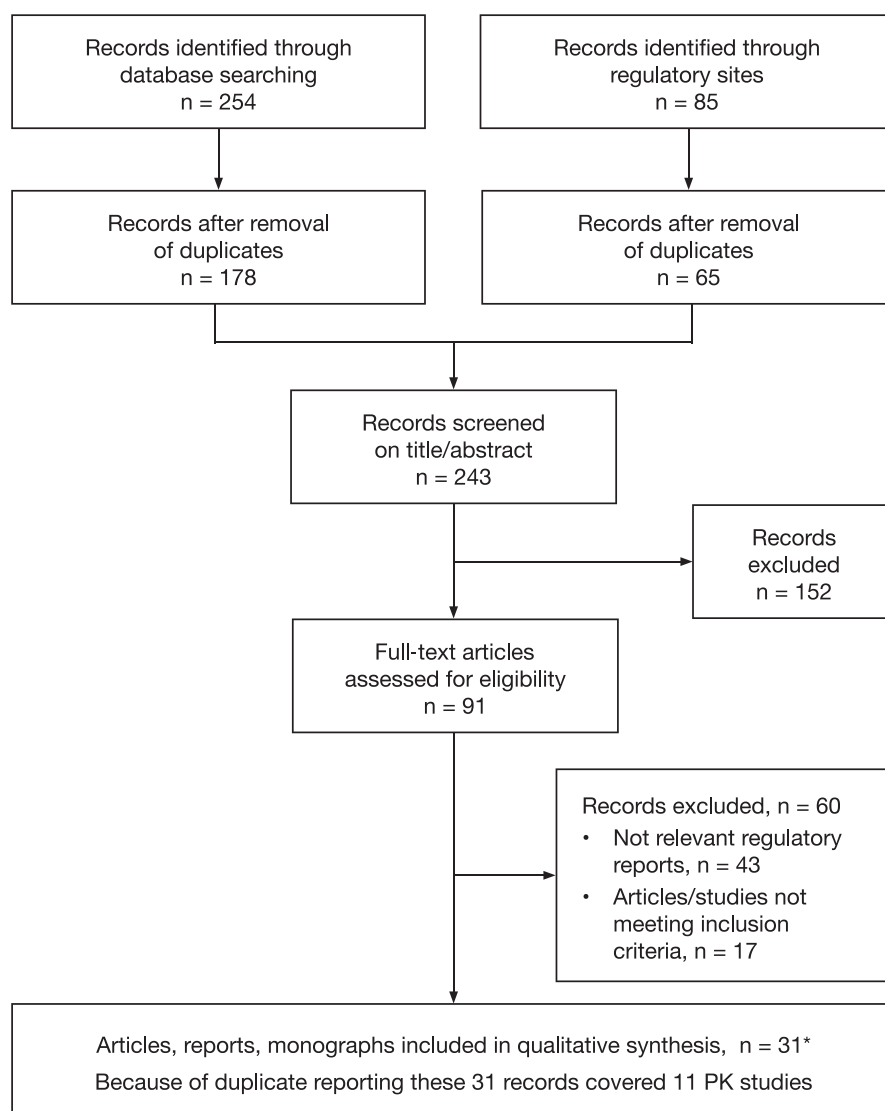


FIGURE 1 Flow diagram depicting the search and selection process used to identify publications and reports on EHL FVIII products. *Additional data were obtained directly from Shire and Bayer in response to information requests, but this did not change the total number of PK studies included. The 31 records selected for further analysis are listed in Supplementary Information, Table S1. EHL, extended half-life



Fc fusion has been used to prolong the half-life of more than 300 therapeutic proteins in the last 25 years—either approved or in development.³⁰ The neonatal Fc receptor (FcRn) delays lysosomal degradation of Fc fusion proteins (and IgG) by cycling them back into circulation, thereby prolonging their plasma half-life.³⁰ Fc fusion technology is employed in the design of rFVIII-Fc.²³

A different approach to improving PK characteristics was used in the design of rFVIII-SingleChain. The heavy and light chains of a truncated B-domain rFVIII were covalently bonded with the aim of improving rFVIII intrinsic stability and increasing its affinity for von Willebrand factor (VWF).³¹

Other new rFVIII products have been designed with different purposes other than to extend half-life (Table 2). For example, BAY 81-8973 and Human-cl rhFVIII have been manufactured, respectively, with the intent of reducing the potential for pathogen transmission and reducing immunogenicity (by avoiding hamster-like epitopes by production in a human cell line).³²⁻³⁴ Both have changes to the glycosylation of rFVIII compared to previous generation proteins (eg anti-haemophilic factor [recombinant]: Kogenate FS), which can influence PK profile.^{32,34,35}

3.2 | EHLs are not bioequivalent to standard rFVIII

Rationally, an EHL rFVIII should have enhanced PK characteristics that are significantly different from standard rFVIII. PK comparisons of exposure to different rFVIII products generally involve an assessment of the area under the curve (AUC) by calculating the ratio of one product to another. As part of the approval process for new rFVIII products, FDA and EMA assess bioequivalence by considering the 90% CIs of the ratio of the AUC for a new product in comparison with its parent compound or other relevant standard rFVIII. If the 90% CIs fall completely between 0.8 (80%) and 1.25 (125%), then the new product is considered bioequivalent to its parent molecule.^{18,36} Having any part of the 90% CI fall outside these limits is sufficient to conclude that a compound is not bioequivalent to 's comparator because there is 90% certainty that *some* individuals will have an AUC ratio that falls outside these bounds. We propose to use these bioequivalence limits to demonstrate the "biodifference" of EHL rFVIII products from standard. For an EHL FVIII, we would ideally expect the *majority* of individuals to have an AUC ratio above the limits of bioequivalence; if the 90% CIs for the AUC ratios fall completely above the window, then there is 90% certainty that the full range of AUC ratios obtained in the treated population will be biobetter than standard rFVIII. Figure 2 depicts the AUC ratio 90% CIs for new rFVIII products relative to this bioequivalence window. Human-cl rhFVIII has been shown to be bioequivalent to Kogenate FS as its 90% CIs for the AUC ratio are fully within the regulatory acceptance limits.³⁵ For rFVIII-SingleChain, the mean AUC ratio in comparison with Advate (1.35) falls close to the upper bioequivalence limit and the lower bound of the 90% CI extends well into the bioequivalence window.²⁵ Thus, while it cannot be concluded that rFVIII-SingleChain is bioequivalent to standard FVIII products, it can also not be concluded that there is 90% confidence that the full range of AUC ratios obtained in the treated population will be above the

bioequivalence window. In contrast, the 90% CIs for AUC ratio for BAX 855 and the 95% CIs for AUC ratio for rFVIII-Fc (90% CIs were not available during the preparation of the manuscript) fall completely above the 1.25 upper limit. The AUC ratios for these 2 products are clearly not equivalent to those of standard FVIII. The results for N8-GP are compromised by the reporting of 95% CI rather than 90% CI and by the use of *multiple* comparator standard FVIII.³⁷ The lower limit of the 95% CI for the AUC ratio for N8-GP compared with a range of prestudy standard FVIII products is 1.23; the 90% CI would be higher and may well fall outside the bioequivalence window.³⁷ For BAY 94-9027 and BAY 81-8973, the results differ slightly according to dose and study, respectively. Following a single 50 IU/kg dose, the lower bound of the 90% CI for the AUC ratio of BAY 94-9027 compared with Kogenate FS falls just outside the bioequivalence window, as shown in Figure 2. At a lower dose of 25 IU/kg, the lower bound of the 90% CI fell within the bioequivalence window; however, this dose is not comparable with doses used in the other studies in our review and is less representative of doses used in clinical practice.²¹ For BAY 81-8937, the results from the LEOPOLD I study show that the 90% CIs for the AUC ratio compared with Kogenate FS in LEOPOLD I are almost completely within the bioequivalence window.³² These data were used in the regulatory authority reports and included a larger and more diverse study population (in terms of age range and race) than the phase 1 Bulgarian PK study, which suggested that the AUC of BAY 81-8973 is increased compared with Advate (GMR (90% CI) 1.48 (1.41-1.55)).³⁸ The Bulgarian study was carried out in a single centre with patients all over the age of 18 years and all of White race.

3.3 | Demonstration of extended half-life and reduced clearance

According to ISTH guidance on study design for PK studies of coagulation factors such as rFVIII,¹⁶ several criteria need to be met for appropriate comparison of their pharmacokinetics. Evidence is required from a PK comparator study wherein both products are tested in the same individual; therefore, the well-known phenomenon of individual differences observed in rFVIII half-lives¹⁵ would not add variance to the calculated results. The relative comparison gained by taking the ratio of the absolute half-life of the study rFVIII to that of the standard rFVIII would cancel out the individual differences. Table 3 depicts the key studies included in this analysis that have a PK comparator design as described by the ISTH guidance. For BAX 855 and rFVIII-Fc, where phase 1 and phase 2/3 studies fulfilled the criteria, the phase 2/3 study, with a larger sample size and as reported in the regulatory documents, is shown in Table 3.

The available evidence from the studies included in this review suggests that rFVIII products designed to be EHLs and with AUC ratio 90% CIs that fall completely outside of the bioequivalence window have reduced clearance (Table 3). However, the clearance data do not indicate a clear cut-off between EHL and standard rFVIII products that lends to a practical definition for an EHL rFVIII product based on this measure alone.

Similarly, as shown in Figure 3, the data do not suggest a clear cut-off for the definition of an EHL FVIII based on half-life extension alone.

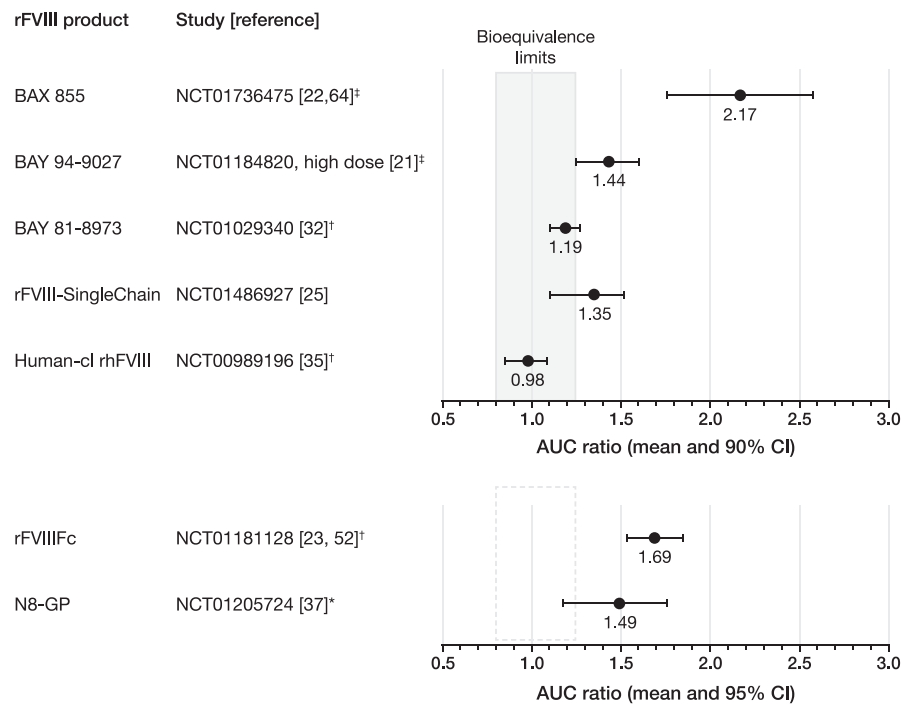


FIGURE 2 AUC ratio of study FVIII: control FVIII for included studies. All data are based on rFVIII measurements from chromogenic assays. Data are from individual clinical studies (as indicated) with different study designs and populations, so the results cannot be directly compared. Filled circles represent the mean (or [†]geometric mean), and bars represent the 90% or 95% confidence intervals (as indicated on the x-axes). The shaded box shows the bioequivalence limits specified by the FDA and EMA for AUC ratio 90% confidence intervals: 0.8 to 1.25.^{18,36} Dashed lines show where these limits fall on the panel with 95% confidence intervals, although it should be noted that they cannot be directly applied to 95% confidence interval data. ^{*}For N8-GP, multiple prior standard rFVIII products were used as comparators in a single study. [‡]Additional data were obtained directly from Shire and Bayer in response to information requests. AUC, area under the curve

BAX 855 and rFVIII Fc, which have AUC ratio 90%/95% CIs that fall completely outside of the bioequivalence window, are among those with the largest half-life extension ratios, and Human-cl rhFVIII, which was bioequivalent to standard rFVIII based on AUC, has a lower half-life than the comparator product (ratio <1); however, the relationship between the AUC data and the half-life data for the other products is less clear. N8-GP demonstrated a relatively high half-life extension ratio. The half-life extension ratios for rFVIII-SingleChain and BAY 81-8973 (both LEOPOLD I—Table 3 and the Bulgaria PK study—GMR [90% CI] 1.16 [90% CI 1.10-1.23]) were <1.2, which does not approach the biological limit imposed by strong binding to VWF, the carrier protein for FVIII.³⁹

4 | DISCUSSION

Prophylaxis with replacement clotting factor concentrates was a key advance for patients with haemophilia A. On balance, alongside protection from bleeds is the demand of frequent infusions because of the relatively short half-life of FVIII. rFVIII products with extended half-lives have an important role to play in advancing the management of haemophilia A by improving patient outcomes and by lessening the burden on patients of inherently time-consuming prophylaxis. It is commonly agreed that adherence is crucial for the efficacy of prophylaxis. As the failure of adherence to prophylaxis

is influenced by the frequency of injections, reducing the number of infusions with EHLs could improve patient outcomes.⁴⁰ Until now, clear distinctions between EHL and standard rFVIII products have not been elucidated and the criteria for classifying an rFVIII as an EHL have not been clearly defined, nor has a critical assessment been conducted to determine which rFVIII products fulfil the requirements.

Although the potential to dispense with 52 infusions per year may be significant from the perspective of a patient, rFVIII products have not seen the clear improvements in half-life observed in EHL-FIX products. The latter have a threefold to fivefold increase in half-life compared to standard FIX concentrates,⁴¹ providing a clear distinction between EHL-FIX and standard FIX. In contrast, rFVIII products may have a ceiling to their half-life extension because of the tight non-covalent association of FVIII in circulation with VWF.^{42,43} While the FVIII interaction with VWF protects it from proteolytic degradation and binding to FVIII clearance receptors (LRP1),⁴⁴ it may also impose a biological limit to the time rFVIII can remain in circulation.⁴⁵ It is hypothesized that a substantial proportion of FVIII is cleared in a complex with VWF⁴³ and thus may limit the ability to extend the half-life of FVIII beyond that of VWF (median 15 hours; range 13-17 hours^{23,39}). Therefore, the half-life extension for categorization as an EHL rFVIII needs to accommodate this limit but still be sufficient enough to ensure that, even with intra- and interperson variance in FVIII pharmacokinetics,^{15,41} the

TABLE 3 Key data extracted from included pharmacokinetic studies and used to assess the rFVIII product fulfilment of the proposed criteria for EHL definition

Product	Study/Reference	N (age [y])	Comparator	Mean ratio (90% CI) (unless otherwise indicated)		
				$t_{1/2}$	AUC _{0-Inf}	Clearance
BAX 855 ^a	NCT01736475 Konkle et al ²² (PROLONG-ATE)	26 (12-65)	Advate	1.51 (1.32, 1.70) ^{64a}	2.17 (1.76, 2.58) ^{64a}	0.55 (0.43, 0.66) ^{64a}
rFVIII-SingleChain ^b	NCT01486927 Klamroth et al ²⁵	27 (18-65)	Advate	1.09 ^c (no CI) ²⁵	1.35 ^c (1.18, 1.6) ²⁵	0.72 ^a mL/(kg·h) (no CI) ²⁵
BAY 94-9027 ^d	NCT01184820 Coyle et al ²¹	14 (2 cohorts of 7 each) (18-65)	Kogenate FS	Cohort 1: 1.43 (1.29, 1.59) Cohort 2: 1.42 (1.31, 1.55) ^d	Cohort 1: 1.41 (1.19, 1.67) Cohort 2: 1.44 (1.28, 1.63) ^d	Cohort 1: 0.696 Cohort 2: 0.70 ^d (no CI)
rFVIIIc	NCT01181128 Mahlangu et al ²³	28 (≥ 12) ²³	Advate	GMR (95% CI) 1.53 (1.34, 1.74) ^{23,52}	GMR (95% CI) 1.69 (1.54, 1.85) ⁵²	GMR (95% CI) 0.59 (0.54, 0.65) ⁵²
BAY 81-8973	NCT01029340 (LEOPOLD 1) Shah et al ³²	26 (>12-65)	Kogenate FS	GMR (95% CI) 1.15 (1.06, 1.24)	GMR (90% CI) 1.19 (1.11, 1.28)	GMR (95% CI) 0.84 (0.77, 0.91)
N8-GP	NCT01205724 Tiede et al ³⁷	25 (≥ 18)	Prior FVIII (Advate, Kogenate, Refacto, or Haemate)	1.56 (95% CI, 1.42, 1.72)	1.49 (95% CI, 1.23, 1.81)	0.67 (95% CI, 0.55, 0.81)
Human-cl rhFVIII	NCT00989196 FDA/Canada ⁶²	22 (12-65) ^{35,63}	Kogenate FS	0.91 ^c (no CI) ³⁵	GMR (90% CI) 0.98 (0.874, 1.107) ³⁵	1.07 ^c (no CI) ³⁵

AUC, area under the curve; CI, confidence interval; Chr, chromogenic assay; GMR, geometric mean ratio; OS, one-stage assay; SD, standard deviation; EHL, extended half-life.

All results in this table are from chromogenic assays. Two phase 1 studies that reported data obtained using the one-stage assay are not included here (NCT01599819, BAX 855 and NCT01027377, rFVIIIc) because data from phase 2/3 studies of the same FVIII products, obtained using the chromogenic assay, were available.

^aData obtained using the chromogenic assay were obtained directly from Shire via a data information request. The pivotal data in Konkle et al reported one-stage assays: mean initial (SD) of: $t_{1/2}$ ratio = 1.4 (0.25) [OS]; AUC ratio = 1.90 (1.53, 2.27); clearance ratio = 0.613 (0.28) [OS].

^bBaseline uncorrected values.

^cCalculated based on published values for absolute half-life of the study rFVIII/absolute half-life of the standard comparator.

^dData including CI were obtained directly from Bayer via a data information request. Cohort 1, 25 IU/kg single dose of rFVIII-FS (n = 6) or BAY 94-9027 (n = 7); cohort 2, 50 IU/kg single dose of rFVIII-FS (n = 7) or 60 IU/kg BAY 94-9027 (n = 7).

majority of individuals can be protected from bleeds with a reduced dosing frequency. While some new rFVIII products may demonstrate some degree of mean half-life extension compared with standard FVIII, a small extension may not be sufficient to allow for at least an additional full day between doses. To further address this point, a separate modelling study has been carried out by a group including some of the authors of this review to identify the minimum half-life extension ratio required for a reduction in dosing frequency while maintaining the proportion of patients with plasma rFVIII levels above 1 IU/dL with no increase in the total weekly dose.⁶⁵ A previously published population PK model for standard rFVIII was used to model the effects of varying half-life extension ratios at different doses and dosing frequencies. The model suggested that a meaningful reduction in the burden of infusions for an EHL rFVIII product (relative to a standard rFVIII) is possible when the half-life extension ratio is 1.3 or greater.

This review is meant to provide guidance to help physicians, patients and health funders to make informed choices when selecting

rFVIII products. Ideally, the classification of standard vs EHL rFVIII products will provide better clarity regarding the rFVIII dosing intervals that can be expected to provide effective prophylaxis for the majority of individuals for the rFVIII products that we have discussed. Towards this end, we recommend the development of a practical definition for EHL rFVIII products. Using the data available at the time of this review, we suggest that both AUC ratio and half-life ratio are needed to provide enough PK evidence to form a strong definition of EHL. Therefore, we propose a definition comprising 3 separate criteria:

1. Designed with technology to extend circulating biological half-life
2. Demonstration of difference from a standard rFVIII comparator for the majority of patients according to proposed "biodifference" criteria based on the lower limit of the 90% CI for the AUC ratio being above the FDA/EMA cut-off for bioequivalence (1.25 or 125%)
3. Having a half-life ratio of 1.3 or higher, based on modelling.⁶⁵

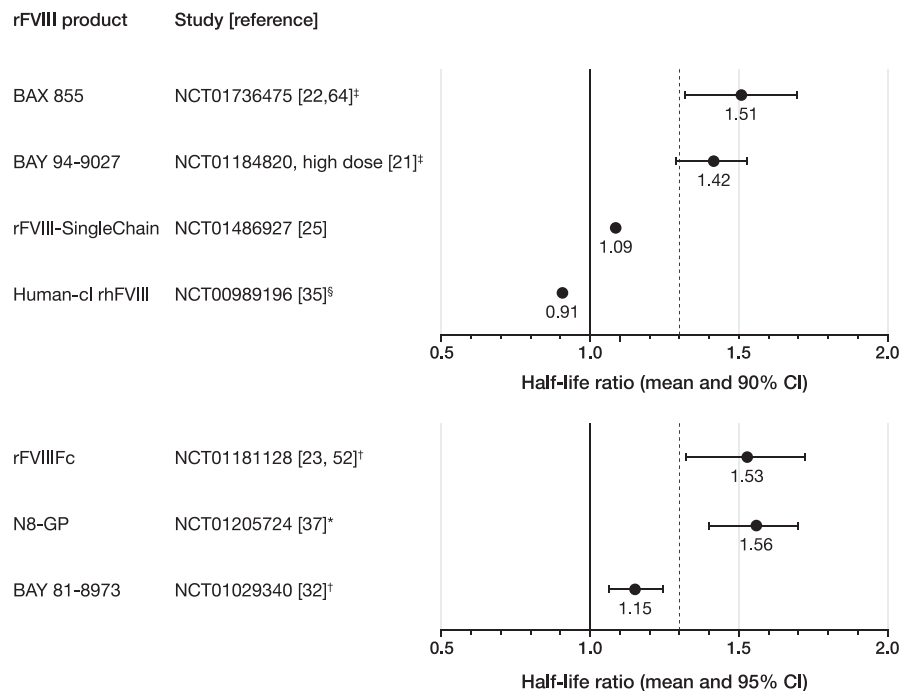


FIGURE 3 Half-life extension ratios of study FVIII: control FVIII for included studies. All data are based on rFVIII measurements from chromogenic assays. Data are from individual clinical studies (as indicated) with different study designs and populations, so the results cannot be directly compared. Filled circles represent the mean (or [‡]geometric mean), and bars represent the 90% or 95% confidence intervals (as indicated on the x-axes), where available. Also, depicted is standard rFVIII half-life (1.0, line) and the half-life extension ratio above which modelling has shown that a meaningful reduction in the burden of infusions for an EHL rFVIII product (relative to a standard rFVIII) is possible without increasing rFVIII dose (1.3, dashed line)⁶⁵. ^{*}Note that for N8-GP, multiple prior standard rFVIIIs were used as comparators in a single study. [‡]Additional data were obtained directly from Shire and Bayer in response to information requests. [§]No confidence intervals were available for Human-cl rhFVIII. EHL, extended half-life

We have found that BAX 855 and rFVIII-Fc clearly meet all 3 of these EHL criteria. BAY 81-8973, Human-cl rhFVIII and rFVIII-SingleChain did not fully meet the criteria; BAY 81-8973 and Human-cl rhFVIII are not designed to be EHLs and have PK characteristics similar to standard rFVIII (Kogenate FS). Although rFVIII-SingleChain is designed to have modified PK characteristics, it cannot be fully differentiated from standard rFVIII (Advate), with 90% CIs for AUC ratio extending below 1.25 and a half-life extension of 1.09 compared to Advate. This suggests that rFVIII-SingleChain may behave like a standard rFVIII in some patients.

For the products in development, BAY 94-9027 and N8-GP, limitations in the data because of study design and reporting differences make interpretation less straightforward; however, current evidence suggests that they both fulfil criteria for EHL rFVIII. They are designed using a technology that has been established for extending half-life (definition criteria 1). Both products show evidence of half-life extension ratios greater than 1.3-fold, thereby meeting criteria 3. The 50 IU/kg dose group of BAY 94-9027 met criteria 2. N8-GP may have met criteria 2 with 90% confidence intervals (only wider, 95% confidence intervals are available) and/or comparison with a single standard rFVIII (multiple different comparators were used). As such, these agents should be classified as EHL rFVIII products despite the limitations imposed by different study designs and reporting.

This guidance provides a straightforward assessment of standard vs currently available EHL rFVIII products, which should ameliorate

clinical decision-making regarding an initial approach for a patient. Reduced dosing frequencies and maintenance of haemostatic efficacy of rFVIII products that meet the EHL definition should be possible for most patients. Given the great variance among individuals' PK responses, an individual's baseline terminal half-life, bleeding phenotype and physical activity level, as well as the rFVIII product half-life should be considered when deciding on an adequate prophylactic EHL rFVIII product dose and infusion schedule.⁴⁶ Importantly, classification of a concentrate can never substitute for careful clinical monitoring of patients, including measurement of rFVIII levels and PK profiles.

A limitation of this analysis is that not all products evaluated had data that allowed for a comparable application of our proposed criteria. There is considerable variation in study design, study population and data reporting that will certainly have influenced the results. As such, no clear comparative conclusions can be drawn. A further limitation is the applicability of this analysis to children, who, in general, have higher clearance and shorter elimination half-lives than adults.^{15,41} It might be expected that the half-life ratio between an EHL rFVIII and a standard FVIII would be the same in children and adults regardless of absolute half-life; however, there could potentially be differences dependent on the mechanism of half-life extension. At the time of writing, there are limited data on the PK characteristics of new rFVIII products in children (<12 years old). Once more evidence is available, a separate analysis should be



conducted for children. Furthermore, because the field is evolving rapidly, the definitions for adults and adolescents proposed in this review will need to be revisited as new products become available. Indeed, overall, the conclusions of this study can only be applied to recently developed and currently available EHL rFVIII. It is clear that if new technologies in future allow half-life extensions of rFVIII independent of its binding to VWF, the definition of EHL may need to be revised or a new category/generation of rFVIII products created. Standard rFVIII products have been defined as first, second, third generation based on their infectious safety and the manufacturing process. The same methodology could be used in future for new EHL rFVIII products with additional beneficial characteristics.

5 | CONCLUSION

Having established an evidence-based definition for EHL rFVIII, these recommendations provide a framework for future assessments of rFVIII products. Furthermore, clarity regarding which rFVIII products fulfil EHL criteria supports rational and informed clinical decisions of physicians and patients when deciding on an EHL rFVIII product. A better understanding of these new tools in the armamentarium for management of severe haemophilia A could potentially enable better outcomes for patients.

AUTHOR STATEMENT

All authors have had full access to the data herein and contributed to the drafting of the manuscript.

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REFERENCES

1. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med*. 1992;232:25-32.
2. Berntorp E. Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens. *Haemophilia*. 2009;15:1219-1227.
3. Baxter Healthcare Corporation. ADVATE, prescribing information [Antihemophilic factor (recombinant), plasma/albumin-free method]. <http://www.fda.gov/downloads/BloodBloodProducts/ucm059095.pdf>. Accessed September 9, 2017.
4. Kreuz W, Escuriola-Ettingshausen C, Funk M, Schmidt H, Kornhuber B. When should prophylactic treatment in patients with haemophilia A and B start? - The German experience. *Haemophilia*. 1998;4:413-417.
5. Tiede A. Half-life extended factor VIII for the treatment of hemophilia A. *J Thromb Haemost*. 2015;13(suppl 1):S176-S179.
6. 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.
7. Bayer Pharma AG. Summary of product characteristics - KOVALTRY. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003825/WC500202781.pdf. Accessed September 9, 2017.
8. Octapharma AB. Summary of product characteristics - Nuwiq. http://ec.europa.eu/health/documents/community-registry/2014/20140722129048/anx_129048_en.pdf. Accessed September 9, 2017.
9. GmbH CB. AFSTYLA, summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004075/WC500224591.pdf. Accessed October 9, 2017.
10. Kessler C, Oldenburg J, Ettingshausen CE, et al. Spotlight on the human factor: building a foundation for the future of haemophilia A management: report from a symposium on human recombinant FVIII at the World Federation of Hemophilia World Congress, Melbourne, Australia on 12 May 2014. *Haemophilia*. 2015;21(suppl 1):1-12.
11. Pierce G. A new era of haemophilia treatment awaits. *EHC Newsletter*, 2016: 48-53.

12. Dunn A. The long and short of it: using the new factor products. *Hematology Am Soc Hematol Educ Program*. 2015;2015:26-32.
13. Morfini M, Cinotti S, Bellatreccia A, et al. A multicenter pharmacokinetic study of the B-domain deleted recombinant factor VIII concentrate using different assays and standards. *J Thromb Haemost*. 2003;1:2283-2289.
14. Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost*. 2016;14:248-261.
15. Bjorkman S, Oh M, Spotts G, et al. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood*. 2012;119:612-618.
16. Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee Communication: The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors. https://cymcdn.com/sites/www.isth.org/resource/group/d4a6f49a-f4ec-450f-9e0f-7be9f0c2ab2e/official_communications/fviiipharco.pdf. Accessed September 9, 2017.
17. European Medicines Agency. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products: draft. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187409.pdf. Accessed September 9, 2017.
18. FDA. Guidance for industry: statistical approaches to establishing bioequivalence. <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf>. Accessed September 9, 2017.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
20. Powell JS, Nugent DJ, Harrison JA, et al. Safety and pharmacokinetics of a recombinant factor VIII with pegylated liposomes in severe hemophilia A. *J Thromb Haemost*. 2008;6:277-283.
21. Coyle TE, Reding MT, Lin JC, Michaels LA, Shah A, Powell J. Phase I study of BAY 94-9027, a PEGylated B-domain-deleted recombinant factor VIII with an extended half-life, in subjects with hemophilia A. *J Thromb Haemost*. 2014;12:488-496.
22. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood*. 2015;126:1078-1085.
23. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123:317-325.
24. BLA. Clinical Review Memorandum: Antihemophilic Factor (Recombinant), rFVIII-SingleChain [Afstyla]. <https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM506511.pdf>. Accessed September 9, 2017.
25. Klamroth R, Simpson M, von Depka-Prondzinski M, et al. Comparative pharmacokinetics of rFVIII-SingleChain and octocog alfa (Advate((R))) in patients with severe haemophilia A. *Haemophilia*. 2016;22:730-738.
26. Fishburn CS. The pharmacology of PEGylation: balancing PD with PK to generate novel therapeutics. *J Pharm Sci*. 2008;97:4167-4183.
27. Stidl R, Fuchs S, Bossard M, Siekmann J, Turecek PL, Putz M. Safety of PEGylated recombinant human full-length coagulation factor VIII (BAX 855) in the overall context of PEG and PEG conjugates. *Haemophilia*. 2016;22:54-64.
28. 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.
29. Baxalta US Inc. ADYNOVATE, Antihemophilic factor (recombinant), PEGylated. Prescribing information. [http://www.fda.gov/downloads/BiologicsBloodVaccines/](http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM472594.pdf)
- BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM506511.pdf. Accessed September 9, 2017.
30. Rath T, Baker K, Dumont JA, et al. Fc-fusion proteins and FcRn: structural insights for longer-lasting and more effective therapeutics. *Crit Rev Biotechnol*. 2015;35:235-254.
31. Schulte S. Innovative coagulation factors: albumin fusion technology and recombinant single-chain factor VIII. *Thromb Res*. 2013;131(suppl 2):S2-S6.
32. Shah A, Delesen H, Garger S, Lalezari S. Pharmacokinetic properties of BAY 81-8973, a full-length recombinant factor VIII. *Haemophilia*. 2015;21:766-771.
33. Garger S, Severs J, Regan L, et al. BAY 81-8973, a full-length recombinant factor VIII: manufacturing processes and product characteristics. *Haemophilia*. 2017;23:e67-e78.
34. Casademunt E, Martinelle K, Jernberg M, et al. The first recombinant human coagulation factor VIII of human origin: human cell line and manufacturing characteristics. *Eur J Haematol*. 2012;89:165-176.
35. Clinical Pharmacology BLA Review (BLA 125555/0), Nuwiq. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM464209.pdf>. Accessed September 9, 2017.
36. Committee for Medicinal Products for Human Use (CHMP). Guideline on the investigation of bioequivalence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed September 9, 2017.
37. Tiede A, Brand B, Fischer R, et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glyco-PEGylated recombinant factor VIII in patients with hemophilia A. *J Thromb Haemost*. 2013;11:670-678.
38. Shah A, Solms A, Garmann D, et al. Improved pharmacokinetics with BAY 81-8973 versus antihemophilic factor (recombinant) plasma/albumin-free method: a randomized pharmacokinetic study in patients with severe hemophilia A. *Clin Pharmacokinet*. 2017;56:1045-1055.
39. Dobrkovska A, Krzenski U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease. *Haemophilia*. 1998;4(suppl 3):33-39.
40. Geraghty S, Dunkley T, Harrington C, Lindvall K, Maahs J, Sek J. Practice patterns in haemophilia A therapy – global progress towards optimal care. *Haemophilia*. 2006;12:75-81.
41. Collins P, Chalmers E, Chowdary P, et al. The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. *Haemophilia*. 2016;22:487-498.
42. Pipe SW. The hope and reality of long-acting hemophilia products. *Am J Hematol*. 2012;87:S33-S39.
43. Denis CV, Christophe OD, Oortwijn BD, Lenting PJ. Clearance of von Willebrand factor. *Thromb Haemost*. 2008;99:271-278.
44. Terraube V, O'Donnell JS, Jenkins PV. Factor VIII and von Willebrand factor interaction: biological, clinical and therapeutic importance. *Haemophilia*. 2010;16:3-13.
45. Pipe SW, Montgomery RR, Pratt KP, Lenting PJ, Lillicrap D. Life in the shadow of a dominant partner: the FVIII-VWF association and its clinical implications for hemophilia A. *Blood*. 2016;128:2007-2016.
46. Hartmann J, Croteau SE. 2017 Clinical trials update: innovations in hemophilia therapy. *Am J Hematol*. 2016;91:1252-1260.
47. Clinical Pharmacology BLA Review (BLA 125566/0) – BAX 855. In: *Division of Hematology, Office of Blood Review and Research*, ed., 2014.
48. Baxalta Canada Corporation. Product monograph including patient medication information – ADYNOVATE (Antihemophilic Factor (Recombinant), PEGylated). https://pdf.hres.ca/dpd_pm/00037118.PDF. Accessed September 9, 2017.
49. Turecek PL, Bossard MJ, Graninger M, et al. BAX 855, a PEGylated rFVIII product with prolonged half-life. Development, functional



- and structural characterisation. *Hamostaseologie*. 2012;32(suppl 1):S29-S38.
50. CSL Behring Canada Inc. Product monograph including patient information – afstyl. <http://labeling.cslbehring.ca/PM/CA/AFSTYLA/EN/AFSTYLA-Product-Monograph.pdf>. Accessed September 9, 2017.
 51. Mei B, Pan C, Jiang H, et al. Rational design of a fully active, long-acting PEGylated factor VIII for hemophilia A treatment. *Blood*. 2010;116:270-279.
 52. Committee for Medicinal Products for Human Use (CHMP). Assessment report: ELOCTA. International non-proprietary name: efmoctocog alfa. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003964/WC500198644.pdf. Accessed September 9, 2017.
 53. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood*. 2012;119:3031-3037.
 54. Clinical Pharmacology BLA Review (BLA 125487/0) – Elocta. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM403743.pdf>. Accessed September 9, 2017.
 55. Biogen Inc. ELOCTATE. Prescribing information. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM400192.pdf>. Accessed September 9, 2017.
 56. Swedish Orphan Biovitrum AB. Summary of product characteristics – ELOCTA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003964/WC500198642.pdf. Accessed September 9, 2017.
 57. Shapiro AD, Ragni MV, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. *J Thromb Haemost*. 2014;12:1788-1800.
 58. Biogen Canada. Product monograph including patient information – ELOCTATE. https://www.biogen.ca/content/dam/corporate/en_CA/pdfs/products/ELOCTATE/2016_07_08-ELOCTATE-PM_E.pdf. Accessed September 9, 2017.
 59. Clinical Pharmacology BLA review (BLA 125574/0) – BAY 81 8973. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM495450.pdf>. Accessed September 9, 2017.
 60. Bayer Inc. Product monograph – KOVALTRY; Health Canada. <http://omr.bayer.ca/omr/online/kovaltry-pm-en.pdf>. Accessed September 9, 2017.
 61. Bayer Pharma AG. Assessment report – EMA/CHMP/71742/2016 – BAY 81 8973. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004147/WC500203048.pdf. Accessed September 9, 2017.
 62. Octapharma Canada Inc. Product monograph – Nuwiq. http://www.octapharma.ca/fileadmin/user_upload/octapharma.ca/Product_Monographs/NUWIQ-PM.pdf. Accessed September 9, 2017.
 63. Octapharma AB. Assessment report – EMA/CHMP/279301/2014 – Nuwiq. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002813/WC500179342.pdf. Accessed September 9, 2017.
 64. Table 1. Summary of PK parameters during treatment with BAX 855 vs Advate (Studies 261201, 261202) – mean. In: Shire, ed., 2016.
 65. Hermans C, Mahlangu J, Booth J, et al. Pharmacokinetic modelling and validation of the half-life extension needed to reduce the burden of infusions compared with standard factor VIII. *Haemophilia*. 2018;24:376-384. <https://doi.org/10.1111/hae.13483>

SUPPORTING INFORMATION

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