Received: 27 November 2023 | Revised: 6 March 2024 | Accepted: 13 March 2024

DOI: 10.1111/hae.15001

Haemophilia WFH WILEY

REVIEW ARTICLE

Classification of recombinant factor VIII products and implications for clinical practice: A systematic literature review

Cihan Ay[1] | Mariasanta Napolitano[2] | Abel Hassoun[3] | Radovan Tomic[4] | Cedric Martin[5] | Wilfried Seifert[6] | Karen Pinachyan[7] | Johannes Oldenburg[8]

[1]Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[2]PROMISE Department, University of Palermo, Palermo, Italy

[3]Haemophilia Treatment Center, Simone Veil Hospital, GH Eaubonne-Montmorency, Eaubonne, France

[4]CSL Behring, Milan, Italy

[5]CSL Behring, Paris, France

[6]CSL Behring, Marburg, Germany

[7]CSL Behring, Brussels, Belgium

[8]Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

Correspondence
Cihan Ay, Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria.
Email: cihan.ay@meduniwien.ac.at

Mariasanta Napolitano, PROMISE Department, University of Palermo, Palermo, Italy.
Email: mariasanta.napolitano@unipa.it

Funding information
CSL Behring

Abstract

Introduction: Consensus over the definition of recombinant factor VIII (rFVIII) product classification in haemophilia A is lacking. rFVIII products are often classified as standard half-life (SHL) or extended half-life (EHL); despite this, no universally accepted definition currently exists. One proposed definition includes half-life, area under the curve, and technology designed to extend half-life; however, the International Society on Thrombosis and Haemostasis defines activity over time as the most intuitive information for building treatment regimens and the World Federation of Hemophilia describes rFVIII product classification in terms of infusion frequency.

Aim: To summarise published data on the clinical and pharmacokinetic criteria used to define rFVIII product classification.

Methods: PubMed and EMBASE database searches of English-language articles (2002–2022) were conducted using search strings to identify the relevant population, intervention, and outcomes (e.g., clinical and pharmacokinetic parameters). Articles then underwent title/abstract and full-text screens.

Results: Among 1147 identified articles, 62 were included. Half-life was the most widely reported outcome with no clear trends or product groupings observed. No clear groupings emerged among other outcomes, including infusion frequency, consumption, and efficacy. As activity over time was reported in few articles, further investigation of its relevance to rFVIII product classification is warranted.

Conclusion: The findings of this systematic literature review suggest that parameters other than half-life might be important for the development of a comprehensive and clinically relevant rFVIII product classification definition. There seems to be an opportunity to consider parameters that are clinically meaningful and useful for shared decision-making in haemophilia A treatment.

KEYWORDS
factor VIII, half-life, haemophilia A, pharmacokinetics, PubMed, review

1 | INTRODUCTION

Haemophilia A is an inherited bleeding disorder caused by a deficiency of functional plasma clotting factor VIII (FVIII), which plays a key role in haemostasis. The current standard of care for haemophilia A is prophylaxis with factor replacement products or non-factor replacement products that aim to reduce the risk of bleeding and prevent joint damage.[1] With many different factor replacement products available, product choice requires shared decision-making by people with haemophilia, their caregivers, and a multidisciplinary team of healthcare professionals.[1] Factors influencing treatment decisions include bleed control and convenience of administration (e.g., infusion frequency).[1] Frequent infusions (3–4 per week) with plasma-derived or standard half-life (SHL) recombinant FVIII (rFVIII) products are often required for prophylaxis, due to their relatively short half-life (~12 h), which can place a significant burden on patients and caregivers.[1,2]

A variety of technologies have been employed to extend the half-life of rFVIII products, which aim to maintain higher trough levels compared with SHL products. Technologies include single-chain design (rVIII-SingleChain, AFSTYLA, CSL Behring), Fc fusion (rFVIIIFc, ELOCTA/ELOCTATE, Swedish Orphan Biovitrum AB), and PEG conjugation (BAY 94—9027, JIVI, Bayer; BAX 855, ADYNOVATE/ADYNOVI, Baxter; N8-GP, ESPEROCT, Novo Nordisk A/S).[1,2] However, these techniques currently only appear to increase half-life by 1.4- to 1.6-fold versus products that do not employ such technologies.[3–5] A possible explanation for this apparent upper limit of half-life extension is the von Willebrand factor (VWF) chaperone effect.[6–9]

The criteria used to classify rFVIII products, which could help guide treatment decisions, remains a topic of debate.[2,10,11] rFVIII products are often classified as either SHL or extended half-life (EHL); despite this, there is currently no universally accepted definition of SHL and EHL products. In 2018, Mahlangu et al., proposed the following definition for EHL products: (i) use of technology designed to extend rFVIII half-life; (ii) not bioequivalent with standard rFVIII comparator (above the U.S. Food and Drug Administration [FDA]/European Medicines Agency [EMA] cut-off of 125% for the 90% confidence intervals [CIs] for area under the curve [AUC] ratio) and (iii) EHL ratio in a pharmacokinetic (PK) comparator crossover study.[2] However, using this definition, only PEGylated or Fc fusion products meet EHL criteria (BAX 855, rFVIIIFc, BAY 94—9027, and N8-GP met all three criteria, while KOVALTRY (BAY 81–8973), NUWIQ (Human-cl rhFVIII), and rVIII-SingleChain did not fully meet the criteria)[2]; also, this categorisation is not consistently followed in the literature, for example, rVIII-SingleChain is considered an EHL product in published papers and described as a 'prolonged half-life' product on the Online Clotting Factor Concentrates (CFC) Registry on the WFH website.[12–14]

The ISTH defines 'activity over time' (e.g., time to 1% [T1%] and time to 5% [T5%]) as the most intuitive information for building treatment regimens and deliver information[10]; however, this parameter is not included in the definition of EHLs proposed by Mahlangu et al. Furthermore, other authors have critiqued the definition proposed by Mahlangu et al., stating that the explanation and meaning behind the 'use of technology designed to extend half-life' is unclear, highlighting that a bioequivalence study is not performed to demonstrate a biodifference, and debating the scientific basis of the 30% half-life increase (arguing that a smaller increase may be 'clinically significant').[11]

In 2018, Hermans et al., proposed that EHL classification should consider both half-life extension and dosing frequency: EHL products should have a minimum half-life extension ratio of 1.3 to provide a reduction in dosing frequency from 3 × per week to 2 × per week versus SHL products.[15] It is also possible that classifications by clinical outcomes (efficacy, safety, or quality of life) may be feasible across rFVIII products. However, currently these are not recommended for FVIII replacement product classification.[2,11]

There is currently a large quantity of PK data on rFVIII products available within the literature; this is used to determine the pharmacological properties of these products but can also be a source of confusion. As debate remains in the literature regarding the most relevant criteria for rFVIII treatment classification, the aim of this systematic literature review was to identify and summarise the currently proposed treatment classifications of rFVIII products for prophylaxis in haemophilia A. This review did not aim to propose an alternative treatment classification system.

2 | MATERIALS AND METHODS

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration CRD42022332191). PubMed and EMBASE database searches of English-language articles published between 1 January 2002 and 7 January 2022 were used to identify articles.

2.1 | Search strategy development

Search terms were developed to cover the relevant population (people with congenital haemophilia A), the intervention (rFVIII replacement products), and the outcomes of interest. These were then combined into a search string: (POPULATION) AND (INTERVENTION) AND (CRITERIA TERM) AND (DATA TYPE). Terms in each category were separated by 'OR' e.g., ("Haemophilia A" OR "FVIII deficiency" OR …) AND (rFVIII OR N8-GP OR …) AND ("Trough level" OR "half-life" OR…) AND ("clinical trial" OR "post-market*" OR …). Full search strings are presented in Table S1.

2.2 | Data extraction and management

The search results retrieved from PubMed and EMBASE using the above strategy underwent an initial screen based on title/abstract, using the below inclusion and exclusion criteria:

- Inclusion criteria:

- Phase I, II, or III trials, population PK models, real-world evidence, full original articles, case reports/case-series, review papers, systematic reviews, or guidelines
- Human subjects diagnosed with inherited haemophilia A receiving prophylactic treatment
- Recombinant supplementation to treat or prevent bleeding episodes
- Approved/licensed products only
- English language abstract or English language full text; and published between 1 January 2002 and 7 January 2022

- Exclusion criteria:
  - Conference abstracts or proceedings, opinion pieces, meta-analyses, editorials, commentaries, or articles not reporting original data
  - Papers that have been retracted
  - Animal models, in vitro, or ex vivo experimental studies
  - Healthy volunteers
  - On-demand treatment only
  - Treating for a condition other than haemophilia A
  - Plasma-derived FVIII supplementation
  - Emicizumab supplementation
  - Non-English abstract and full text

A second screen was then undertaken using the same inclusion/exclusion criteria, by reviewing the full text of the publications. All publications identified in this manner were carried forward to the data extraction step.

After final review of the full texts, all relevant data were extracted from selected articles based on the inclusion/exclusion criteria. In addition to general information describing type of publication and study details (type, size, location, and duration), additional outcome measures were extracted where available.

2.3 | Outcomes

Primary outcome measures included PK parameters (half-life, T1%, AUC, mean residence time [MRT], clearance, time to maximum plasma concentration [T_{max}]), injection frequency/dose regimen, consumption, and indications. Secondary outcome measures included efficacy (annualised bleeding rate [ABR], annualised spontaneous bleeding rate [AsBR], annualised joint bleeding rate [AjBR]), safety, and quality of life parameters.

3 | RESULTS

3.1 | Study characteristics

3.1.1 | Included studies

A total of 1147 articles were identified using the search strings (1022 in PubMed, 125 in EMBASE). Of the 1147 articles, 887 were excluded at title/abstract screening, and a further 198 were excluded at full-text screening; reasons for exclusion are shown in Figure 1. Overall, 62 articles met the inclusion criteria, of which 57 were prospective studies and 5 were retrospective. A full list of included articles is included in the Supplementary Materials.

3.1.2 | Reported data

Forty-four studies reported data on a single rFVIII product: 8 with BAY 81−8973, 6 with rFVIIIFc, 6 with ADVATE (rFVIII), 6 with N8-GP, 5 with KOGENATE/KOGENATE-FS (BAY 79−4980), 3 with REFACTO (BDDrFVIII), 3 with rVIII-SingleChain, 2 with BAX 855, 1 with BAY 94−9027, 2 with Human-cl rhFVIII, 1 with GREENGENE (Green Cross Corporation), and 1 with NOVOEIGHT (N8). Eighteen studies compared data from 2 or more rFVIII products.

Very few studies commented on or mentioned the classification of products (SHL/EHL or standard-acting [SA]/longer acting [LA]), with 12 studies describing the use of an SHL/EHL product and 4 studies describing the use of 'standard-', 'long-', or 'longer-acting' products. Of these studies, 5 referenced their claims of whether products were SHL/EHL/SA/LA, with 4 referencing Mahlangu et al.[2]

All 62 articles reported PK data, 35 described efficacy data, 46 included safety data, and 5 reported quality of life data. Most articles reported measured PK data (53 studies), and the remaining studies utilised simulated or population PK data. All articles reported on previously treated patients (PTPs), and 1 also reported on previously untreated patients (PUPs). Fifty-eight studies reported age data, and the majority of studies included adult data with 11 studies reporting paediatric data (average age ≤ 12 years). Eleven (18%) of the 62 articles reported real-world evidence (RWE), whereas the majority (51 articles) reported clinical data. RWE tended to be reported more recently than clinical data: RWE articles were published from 2009 to 2020, the majority of which (9/11) were published in 2017 onwards, whereas clinical articles were published from 2002 to 2022.

3.2 | Primary outcomes

3.2.1 | Half-life

In total, 53 studies described half-life data. No clear groupings by half-life were seen, with some overlap between products and wide variations in half-life of each product observed between studies (Figure 2; Table S2). Studies directly comparing more than 1 product reported that rFVIII had a longer half-life than RECOMBINATE (antihemophilic factor [recombinant] [rAHF], Takeda) (12.0 h vs. 11.2 h, respectively), and BDDrFVIII (13.6 h vs. 13.0 h), and shorter half-life than BAX 855 (10.4 h vs. 14.3 h), rVIII-SingleChain (11.6 h vs. 14.0 h), rFVIIIFc (12.4 h vs. 19.0 h), BAY 79–4980 (10.18 h vs. 12.24 h), and BAY 81−8973 (12.0 h vs. 13.9 h).

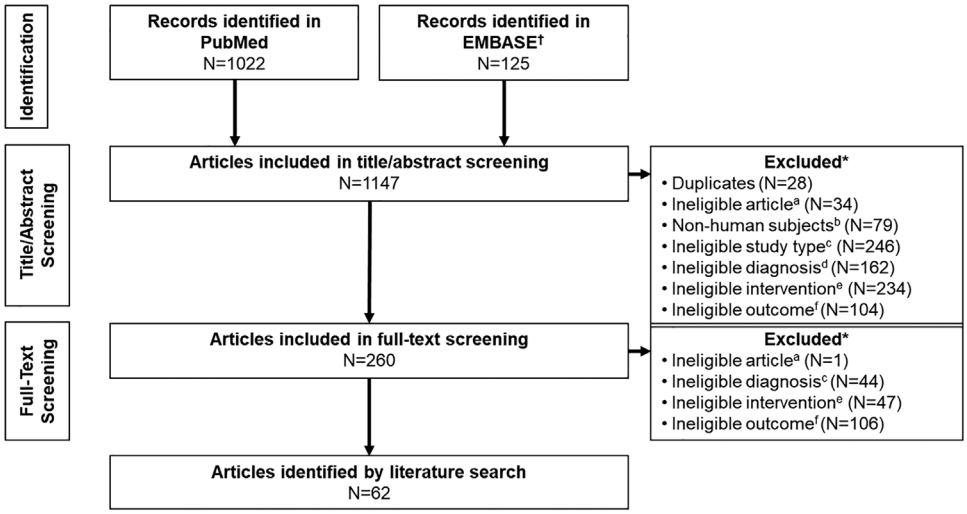

FIGURE 1 PRISMA flow diagram. *Some articles met multiple criteria. †Search string removed PubMed articles. [a]Ineligible articles consisted of manuscripts not written in English language were ineligible article types (e.g., congress proceedings), or were retracted articles. [b]Exclusions for non-human subjects included any study using animals or animal tissues or in vivo, in vitro, or ex vivo studies. [c]Ineligible study types included those that were based on cost analyses, meta-analyses, or editorials. [d]Any study in which patients were not diagnosed with haemophilia A, or multiple diagnoses were present (e.g., haemophilia A and haemophilia B patients in the same group). [e]Studies in which patients were not treated with a rFVIII product, were treated with unlicensed products, or where the product was not named. [f]Studies that did not provide relevant PK outcomes, for example, trough level, half-life, AUC and so forth. AUC, area under the curve; PK, pharmacokinetic; rFVIII, recombinant factor VIII.

3.2.2 | Time to 1% (T1%)

Only 14 articles reported T1%, 5 for rFVIIIFc, 4 of which reported data for rFVIII, 4 for BAY 81–8973, 2 for BAY 94–9027, 2 for BAX 855, 1 for BAY 79—4980, 1 for N8-GP, and 1 for rVIII-SingleChain (Table 1). There was heterogeneity in reporting between studies (e.g., median vs. mean values) and by product dose. The highest reported T1% was for N8-GP (median ~6.6 days [dose: 50 IU/kg]) followed by rVIII-SingleChain (median 5.1 days [dose: 50 IU/kg]).

3.2.3 | AUC, MRT, clearance, trough level, T_{max}

Of the 62 included articles, 42 reported clearance, 37 reported AUC data, 23 reported MRT, 18 reported PK data relating to trough levels, and 3 reported T_{max}. No clear trends or groupings of products were observed in these outcomes (Table S2).

Clearance ranged:

- 0.021 to 0.0276 dL/h/kg for BAX 855
- 0.0212 to 0.0305 dL/h/kg for rVIII-SingleChain
- 0.0168 to 0.025 dL/h/kg for rFVIIIFc
- 0.0144 to 0.020 dL/h/kg for BAY 94—9027

AUC ranged:

- 994 (dose: 25 IU/kg) to 1800 IU h/dL (65 IU/kg) for rFVIII
- 1850 (variable dose) to 2030 IU h/dL (50 IU/kg) for rVIII-SingleChain
- 1892 (37.6 IU/kg) to 2725 (60 IU/kg) IU h/dL for BAX 855
- 1480 (25 IU/kg) to 2800 (65 IU/kg) IU h/dL for rFVIIIFc
- 1577 (25 IU/kg) to 4723 (60 IU/kg) IU h/dL for BAY 94—9027

MRT values ranged from 12.3 (Human-cl rhFVIII, 15 to 50 IU/kg) to 27.7 (BAY 94–9027, 60 IU/kg) h, with variation between studies of the same product and overlap between different products. In the 3 studies reporting T_{max}, median values were: GREENGENE, .50 h (baseline), .33 h (6 months); rFVIII, .58 h (vs. .68 h with rVIII-SingleChain; $p = .0014$); and rFVIII, age < 6 years: 1.04 h; 6–12 years: 1.00 h; > 12 years: .27 h.

3.2.4 | Infusion frequency

Although no clear differences in infusion frequency were seen, with overlap between products, average values ranged from 1 (N8-GP [75 IU/kg] and BAY 94–9027 [60 IU/kg]) to 3.5 (rFVIII [20–40 IU/kg] and human-cl rhFVIII [median 95.0 IU/kg/week]) infusions per week among adults (Figure 3; Table S3). Twelve studies reported only data following a single dose; the remaining studies reported data from prophylactic treatment or prophylactic treatment in combination with on-demand and/or single dose.

3.2.5 | Consumption

Consumption data was reported in 39 studies (either as median [IQR], mean [SD], or both). In one comparison study, patients switched from rFVIIIFc to BAX 855, maintaining the same dose and infusion

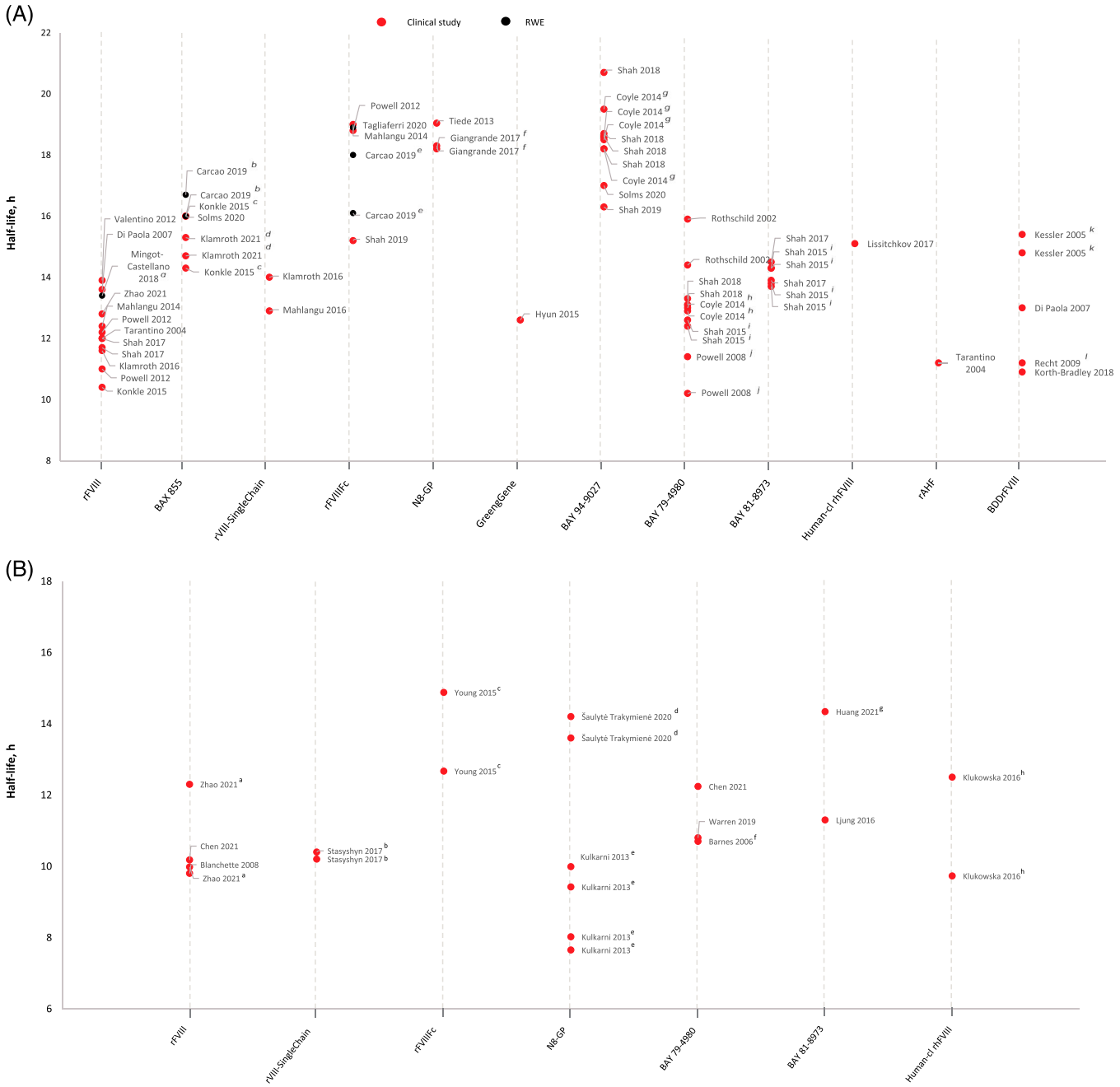

FIGURE 2 Mean half-life of rFVIII products (A) adult data*, (B) paediatric data. *Adult data includes some adolescent patients. (A): Adult data: a. Only data for patients aged > 15 y included. b. CA: 16.0 h; OSA: 16.7 h. c. After single dose: 14.3 h; after 50 EDs and after 6 months of prophylactic treatment: 16.0 h. d. In the 1%–3% FVIII activity target trough level arm: 13.4 h; in the 8%–12 % arm: 14.7 h. e. CA: 18.0 h; OSA: 16.1 h. f. Two PK sessions: 18.3 and 18.2 h, respectively. g. 25 IU/kg, single dose: 18.2, 25 IU/kg, 2× wk: 18.6, 25 IU/kg, single dose: 18.5, 60 IU/kg, 2x/wk: 19.5. h. 12.9 h with 25 IU/kg SD; 13.0 h with 50 IU/kg SD. i. BAY 79–4980: single dose OSA, 12.2 h, single dose CA, 12.0 h; BAY 81–8973: Part A single dose OSA: 14.1 h, Part B multiple dose OSA: 13.8 h, Part A single dose CA: 13.8 h, Part B multiple dose CA: 13.2 h. j. High-dose group: 10.2 h; low-dose group 11.4 h (high-dose [35 IU FVIII kg−1 in 22 mg liposomes kg−1 (2450 IU in a 17.1 mL volume for a 70 kg person)] or low-dose [35 IU FVIII kg−1 in 13 mg liposomes kg−1 (2450 IU in a 9.8 mL volume for a 70 kg person)]). k. Formulation BDDrFVIII-A, 15.4 h; formulation BDDrFVIII-B, 14.8 h. L. Age (years), Median (range) Study 1: 24 (12–60); Study 2: 19.0 (7–70). (B). Paediatric data: a. < 6 years: 12.3 h, 6–12 y: 9.98 h. b. 0–6 y: 10.4 h, ≥6–12 y: 10.2 h. c. < 6 y: 12.67 h (11.23–14.11), 6– < 12 y: 14.88 h. d. 0–5 y: 13.6 h, 6–11 y: 14.2 h. e. CA: 0–5 years: 9.99 (1.71), 6–11 y: 9.42 (1.52), OSA: 0–5 y: 7.65 (1.84), 6–11 y: 8.02 (1.89). f. Includes adolescents (mean age: 12.8 y [range: 4.4–18.1]). g. Includes adolescents (mean age: 7.41 y [range: 2.95–18.27]). h. OSA: 12.50 h, CA: 9.73 h. CA, chromogenic assay; ED, exposure days; h, hours; OSA, one-stage assay; PK, pharmacokinetic; RWE, real-world evidence; SD, single dose; y, years.

frequency; another comparison study reported similar median consumption between products (BAY 79–4980: 60.6 IU/kg/week, BAY 81–8973: 61.6 IU/kg/week). No clear pattern of consumption emerged across the products (Table S3).

3.3 | Secondary outcomes

3.3.1 | Efficacy

Of the 62 included articles, 35 reported at least 1 of the following efficacy outcomes: ABR, AsBR, and AjBR. ABRs were reported for rFVIII, BAX 855, rVIII-SingleChain, rFVIIIFc, N8-GP, BAY 94–9027, BAY 79–4980, BAY 81–8973, Human-cl rhFVIII, and BDDrFVIII. Twenty-four articles reported AjBR and 26 studies reported AsBR. Twenty-one articles reported zero bleeding rates (0 ABR). No clear groupings by efficacy were observed, with overlap between products and no apparent trends in relation to half-life and infusion frequency (Figure 3; Table S4).

3.3.2 | Safety

Forty-two of the 62 included articles reported adverse event (AE) data. Safety studies reporting serious and non-serious adverse events (SAEs) were available for rVIII-SingleChain, rFVIII, BAX 855, rFVIIIFc, N8-GP, GREENGENE, BAY 94–9027, BAY 79–4980, BAY 81–8973, Human-cl rhFVIII, BDDrFVIII, and N8. Treatment-related SAEs were reported for rFVIII, N8-GP, GREENGENE, BAY 94–9027, rVIII-SingleChain, BDDrFVIII and BAX 855. No deaths or thrombotic events were reported across all publications.

Forty-two studies reported on inhibitor development, including events of inhibitor development after exposure to rFVIII, BAX 855, N8-GP, GREENGENE, BAY 79–4980, and BDDrFVIII. Only one study reported on using the product (BDDrFVIII) for immune tolerance induction (ITI). There were no safety data reported that suggest any clear differences between products or groupings of products.

3.3.3 | Quality of life

Only 5 of the 62 included studies reported quality of life outcomes (1 with rFVIIIFc, 1 with BAX 855, 1 with N8-GP, and 2 with rFVIII). Due to the very low proportion of studies that reported quality of life, relevance cannot be reached using this set of data.

4 | DISCUSSION

This systematic literature review aimed to identify and summarise the published literature on the treatment classification of rFVIII products for prophylaxis in people with congenital haemophilia A. Overall, the findings from the 62 studies included in this analysis support the need for reporting of outcomes that might be important to treatment classification more widely. For the primary objective of summarising PK parameters used to define rFVIII classification, no clear groupings emerged based on half-life, T1%/T5%, infusion frequency, trough level, AUC, MRT, clearance, T_{max}, or consumption. Similarly, for the secondary outcomes, no clear groupings emerged based on efficacy or safety; for quality of life, the small number of studies reporting this parameter did not allow for any relevant conclusions to be reached.

Half-life was the most studied PK parameter and was reported in most of the articles included in this review (53/62), but rFVIII product half-lives varied widely (including between studies of the same product), with overlap between products. Some product half-life data also varied from their respective SmPCs (e.g., rFVIIIFc SmPC half-life is 19.0/20.9 h vs. 14.5—19 h among the studies included in this analysis).[3,28,29] This could be due to the adoption of different methodologies (e.g., sampling design, population PK analysis vs. non-population PK, and limit of quantification), making it difficult to compare data between studies and draw firm conclusions. There also appears to be discrepancy between half-life calculated using real-world and clinical trial data, for instance the lowest reported half-life for rFVIIIFc in this systematic literature review of 14.5 h was reported in a real-world study,[29] which is in line with a recently published real-world study reporting data on individuals switching to rFVIIIFc from SHL products (15.0 h).[30] One suggestion from Delavenne and Dargaud,[11] is to standardise PK studies, to ensure similar parameters are collected and to enable more accurate comparisons between studies; this approach is already in place for regulatory studies.

As discussed in a recent position paper, including indirect comparison studies, some individuals show better PK with one product versus another, despite no significant differences in mean values.[31] This highlights the potential importance of personalised prophylaxis, where rFVIII product choice is tailored based on each patient's individual PK. In the studies included in the present review that directly compared two or more products, rFVIII was often used as a comparative product. The variation between reported measured half-life for rFVIII (9.88—16.3 h), and a shorter half-life observed in paediatric versus adult data, meant these comparisons were not standardised. Additionally, parameters influencing PK that are not taken into consideration in this analysis are under constant re-evaluation. For example, the effect of previous FVIII inhibitor development.[32] Similarly, the lack of emergence of clear groups by infusion frequency could be due to flexible choice of dosing regimen, making it difficult to compare data and draw meaningful conclusions.

Although considered the most intuitive PK parameter for building treatment regimens and communication with patients,[10] T1% and T5% were only reported in a small number of the included articles (12/62). Heterogeneity in reporting between studies (e.g., median vs. mean values), and by product dose meant that treatment classification by T1% could not be evaluated accurately.

For clinical outcomes, current proposed treatment classification papers do not mention efficacy when defining how FVIII replacement products should be classified.[2,11] Improvements in the structure of FVIII replacement products, regardless of classification, and the choice

TABLE 1 PK results: Activity over time.

Study	Population	Product	Dose (IU/kg unless otherwise stated)	Time to 1%	Time to 5%	Methodology
Arvanitakis *et al.* (2022)[16]	PTPs (adult; median 40.5 [26.0−−48.8] years)	BAY 81−8973	At the discretion of the investigator	Median (IQR) 96.5 h (71.9−145.2) ~4.0 days	–	Simulated/PopPK (WAPPS-Hemo)
Carcao *et al.* (2019)[17]	PTPs (adolescent; median 15.5 [12.1−18.4] years)	BAX 855	Mean (range) 38.3 (29.7−50.4)	Mean (range) OSA: 112.2 h 72.0−163.5) ~4.7 days CA: 112.9 h (70.4−166) ~4.7 days	Mean (range) OSA: 67.7 h (42.8−100.5) ~2.8 days CA: 70.3 h (42.6−105.0) ~2.9 days	Measured ($n = 25$)
		rFVIIIFc	Mean (range) 39.3 (30.3−52.6)	Mean (range) OSA: 108.3 h (66.7−166.5) ~4.5 days CA: 115.2 h (75.6−178.5) ~4.8 days	Mean (range) OSA: 65.4 h (39−106) ~2.7 days CA: 67.2 h (41.8−110.5) ~2.8 days	
Mahlangu *et al.* (2014)[3]	PTPs (adult; median 30 [12−65] years)	rFVIII	50	Mean (SE) 3.3 days (3.0−3.7)	–	Measured ($n = 165$)
		rFVIIIFc	50	Mean (SE) 4.9 days (4.4−5.5)	–	
Megías-Vericat *et al.* (2019)[18]	PTPs (adult; median 33.0 [IQR: 26.5−42.5] years)	rFVIII	Median (IQR) 69 (56.3−76.5) IU/Kg/week	Median (IQR) 72.0 h (63.5−87.5) 3.0 days	–	Simulated/PopPK (myPKFiT)
Megías-Vericat *et al.* (2019)[19]	PTPs (incl. paediatric; median 30.1 [10−50] years)	BAY 79−4980	Median (IQR) 60.6 (43.5−74.3) IU/Kg/week	Median (IQR) 108.8 h (93.5−148.5) ~4.5 days	Median (IQR) 49.6 h (39.6−61.0) ~2.1 days	Simulated (WAPPS-Hemo)
		BAY 81−8973	Median (IQR) 61.6 (43.5−74.4) IU/Kg/week	Median (IQR) 101.0 h (94.0−133.5) ~4.2 days	Median (IQR) 52.6 h (46.0−60.6) ~2.2 days	
Mingot-Castellano *et al.* (2018)[20]	PTPs (> 15 y; median 30 [16−53] years)	rFVIII	Not reported	Median (IQR) 69.0 h (60.0−80.0) ~2.9 days	–	Simulated/PopPK (myPKFiT)
				Mean (SD) 70.4 h (16.0) ~2.9 days	–	
	PTPs (≤15 y; median 9 [7−15] years)	rFVIII	Not reported	Median (IQR) 51.0 h (47.5−55.0) ~2.1 days	–	
				Mean (SD) 50.9 h (4.4) ~2.1 days	–	
Santoro *et al.* (2020)[21]	PTPs (incl. paediatric; median 22.0 [13.0−40.0] years)	BAY 81−8973	50	Median (5−95% quantiles) 87.6 h (59.4−153.0) ~3.7 days	–	Simulated/Pop PK (WAPPS-Hemo)

(Continues)

TABLE 1 (Continued)

Study	Population	Product	Dose (IU/kg unless otherwise stated)	Time to 1%	Time to 5%	Methodology
Shah *et al.* (2019)[22]	PTPs (adult; mean 36.0 years)	BAY 94–9027	60	Median 117 h ~4.9 days	Median 79.1 h ~3.3 days	PopPK
		rFVIIIFc	60	Median 104 h ~4.3 days	Median 67.4 h ~2.8 days	
Shah *et al.* (2017)[23]	PTPs (adult; mean 37.3 [13.8] years)	BAY 81–8973	25	Median (5%–95% quantiles) 80.5 h (50.5–122.5) ~3.4 days	Median (5%–95% quantiles) 49 h (30–74.5) ~2.0 days	Simulated/PopPK
		rFVIII	25	Median (5%–95% quantiles) 62.5 h (39.5–100) ~2.6 days	Median (5%–95% quantiles) 34.5 h (24–57) ~1.4 days	
Shapiro et al. (2017)[24]	PTPs (incl. adolescent; median 30 [12–65] years)	rFVIIIFc	25, 50, 65	Median predicted Single dose 25 IU/kg: 96 h (4 days) Single dose 65 IU/kg 120 h (5 days)	Median predicted Single dose 50 IU/kg: 72 h (3 days) Prophylaxis Q3D, Q4D, and Q5D, 50 IU/kg: 72 h (3 days)	PopPK
Solms *et al.* (2020)[25]	PTPs (adult; median 33.3 [23–56] years)	BAY 94–9027	50 (actual median dose: 54.3)	Median 120 h 5.0 days	Median 77.5 h ~3.2 days	PopPK
		BAX 855	50 (actual median dose: 61.4)	Median 104 h ~4.3 days	Median 68.1 h ~2.8 days	
Tagliaferri *et al.* (2020)[26]	PTPs (incl. paediatric; mean 30.5 [15.5] years)	rFVIIIFc	Weekly mean (1 SD) First: 96.2 (13.1) Last: 84.9 (19.4)	–	>5% at 48 h (2 days) (except 1 adult and 2 paediatric patients)	Measured ($n = 20$)
Tiede *et al.* (2013)[4]	PTPs (adult; median 36.5 [20–60] years)	N8-GP	25, 50 or 75	Mean (SD) Median (range) 25 IU/kg: 3.91 days (1.09) 3.16 days (2.90–5.20) 50 IU/kg: 6.53 days (1.41) 6.58 days (3.56–7.87) 75 IU/kg: 5.49 days (1.57) 5.93 days (3.33–7.71) Total: 5.73 days (1.6) 6.09 days (3.42–8.35)	–	Measured ($n = 26$)
Zhang *et al.* (2017)[27]	PTPs (incl. paediatric)	rVIII-SingleChain	20, 30, 40 or 50	Maintained above 1%, median 25 IU/kg: 4.3 days 30 IU/kg: 4.6 days 40 IU/kg: 4.9 days 50 IU/kg: 5.1 days	–	Simulated/PopPK

Abbreviations: CA, chromogenic assay; h, hours; IQR, interquartile range; OSA, one-stage assay; PK, pharmacokinetic; PopPK, population PK; PTP, previously treated patients; SD, standard deviation; SE, standard error; y, years.

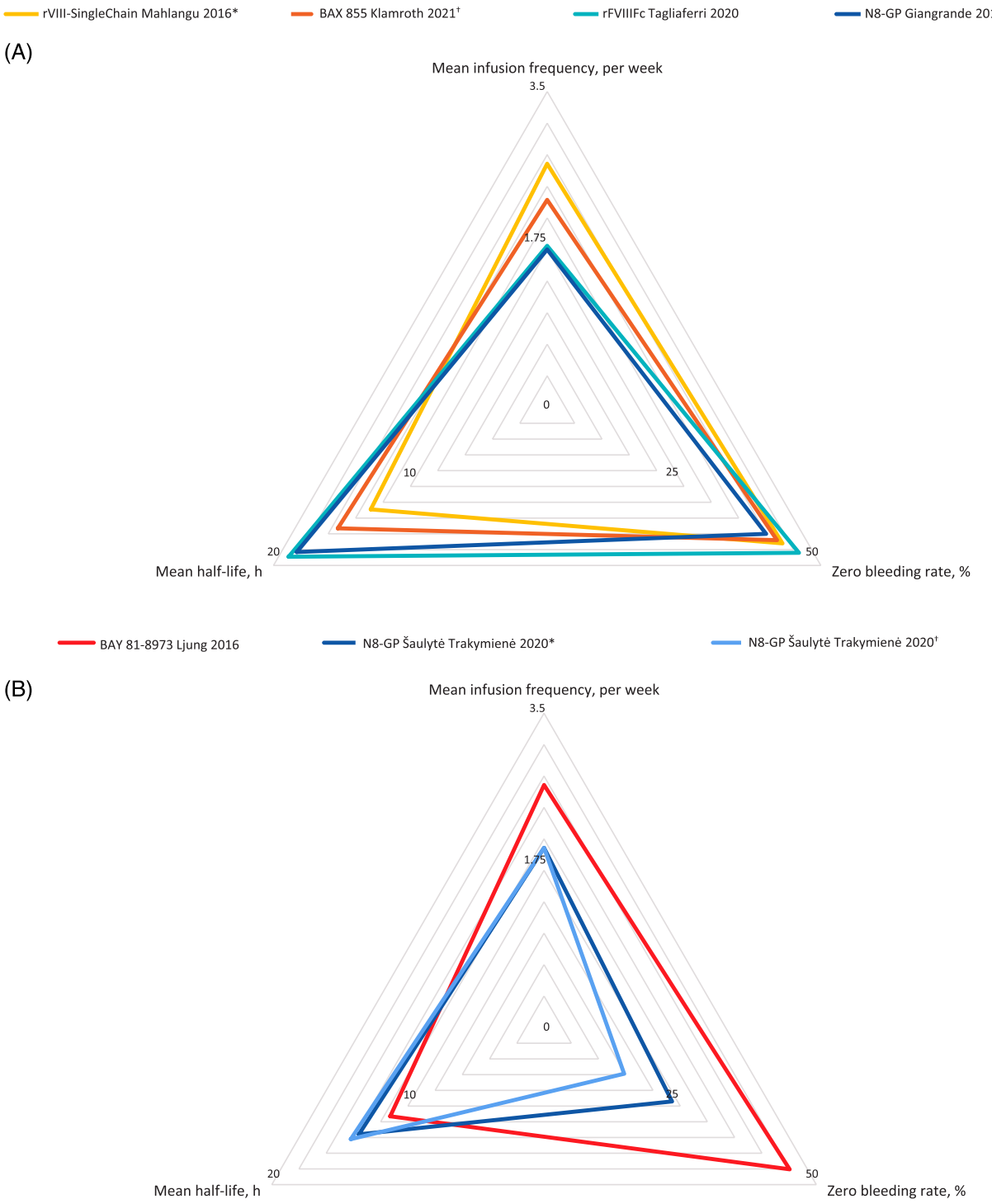

FIGURE 3 Infusion frequency and efficacy (A) adult/adolescent data, (B) paediatric (< 12 years) data. (A). Adolescent defined as 12–18 years; Tagliaferri et al 2020 included 2 children (10% of study population, ages 9 and 10).[26] *11/146 participants had 'other' regimen; mean calculated using those receiving 2×, 3×, and 3.5× weekly treatment. †1%–3% target group. (B) *0–5 y. †6–11 y. h, hours; y, years.

of treatment paradigm allow for the possibility of patients reaching an AsBR of 0; therefore, these parameters might not be relevant for treatment classification. Similarly, the proposed treatment classification by Mahlangu et al., did not mention safety when defining how products should be classified.[2] These observations are consistent with our findings in this study, which also showed that no pattern of efficacy or safety differences between products emerged.

Due to the very low proportion of studies that reported quality of life, its relevance for classification cannot be confirmed from this set of data. However, it is likely to be relevant for this purpose as

a reduced frequency of dosing is likely to directly affect quality of life. For example, patients who switched from their previous rFVIII to rFVIIIFc prophylactic treatment reported significantly improved treatment satisfaction as revealed by the Hemo-Sat scores in all domains and particularly related to the pharmacological therapy (ease and convenience, efficacy, burden, general satisfaction), as well in the total score.[26] Similarly, paediatric patients switching from their previous FVIII product to N8-GP prophylactic treatment reported improvement in quality of life.[33] Using patient-related outcome measures to classify rFVIII products may provide a more patient-centric perspective, thereby helping to assess the real-world impact of a rFVIII product on patients.

EMA guidelines state PK trials for new FVIII products should record incremental recovery, in vivo half-life, AUC, and clearance.[34] Although half-life was reported in the majority of papers (53/62), ISTH guidance states that time to a desired activity level (i.e., T1%/T5%) is the most intuitive information for building treatment regimens,[10] yet this parameter was only reported in 14/62 studies included in the present analysis.

The suggested threshold for increase in half-life of ≥ 1.3 for classification as an EHL product[15] is considerably lower than seen with the new class of FVIII EHL (BIVV001; efanesoctocog alfa, rFVIIIFc-VWF-XTEN, Sobi/Sanofi),[35] where a 3–4 × increase has been observed, and factor IX EHL product classification, where a 3–5 × increase has been observed.[36] In addition, although 18 studies in the current analysis compared more than 1 product, rFVIII was often used as a comparator and its reported half-life varied (10.2–13.6 h) across these studies, impacting the ratio of improved half-life. Furthermore, as described by Delavenne and Dargaud,[11] increases in half-life by 30% might not necessarily result in infusion frequency reductions by ≥ 1 day versus reference treatment in most patients.

The findings of the present study suggest that there appears to be a need for standardization of PK measurements among future rFVIII studies. While SmPC data may be useful for comparing products, randomised comparator studies could be more accurate and therefore preferred. Also, analyses of patients switching from a rFVIII product to another, particularly in real-world studies, may be helpful in informing treatment decisions by overcoming the limitations of comparing PK data between different studies. For instance, a recent RWE study of patients switching from SHL products to rVIII-SingleChain in France found improved PK versus clinical trial data.[14] Real-world data are particularly relevant for rare diseases, confirming effectiveness of treatments, taking 'non-ideal' patients into consideration, and enabling assessment of subpopulations and small populations.

Limitations of this study include the scarcity of paediatric data; as such, the applicability of the results to children is unknown (rFVIII in these patients generally has a higher clearance and shorter half-life than in older patients).[36,37] Also, there is under-reporting in the literature for several parameters of interest (e.g., quality of life, T1%/T5%, T_{max}); therefore, robust conclusions were unable to be drawn on the relevance of these for rFVIII classification. Finally, there was considerable variation in methodologies (e.g., measured vs. population PK) and study populations across the 62 included articles.

This review did not aim to propose an alternative treatment classification system, but to take a broad approach to the literature to identify and summarise the currently proposed treatment classifications of rFVIII products. This study shows that inter-study comparisons are not reliable for establishing a classification. No clear trends or groupings in half-life data were observed, suggesting that parameters other than half-life, such as T1% or T5%, might be important for the development of a comprehensive and clinically relevant rFVIII product classification definition. As T1%/T5% was reported in only a small proportion of studies included in this systematic literature review, further investigation of the relevance of this parameter to rFVIII product classification is warranted.

5 | CONCLUSION

There seems to be an opportunity to consider rFVIII classification parameters that are clinically meaningful and useful for the improvement of dialogue between patients and physicians and shared decision-making.

ACKNOWLEDGEMENTS

Medical writing support was provided by Meridian HealthComms Ltd (Macclesfield, UK) in accordance with Good Publication Practice guidelines and funded by CSL Behring.

CONFLICT OF INTEREST STATEMENT

Cihan Ay has received consultancy and/or speaker fees from Bayer, Novo Nordisk, Takeda, CSL Behring, Pfizer, Octapharma, Roche, LFB, and Swedish Orphan Biovitrium. Mariasanta Napolitano has acted as consultant for Bayer, Novo Nordisk, Sobi, and Kedrion, and has received speaker fees from Takeda, CSL Behring, Bayer, Novo Nordisk, Kedrion, Novartis, Amgen, and Pfizer. Abel Hassoun has acted as a consultant for Bayer, CSL Behring, and Sobi. Radovan Tomic, Cedric Martin, Wilfried Seifert, and Karen Pinachyan are employees of CSL Behring. Johannes Oldenburg has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai, CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum and Takeda.

DATA AVAILABILITY STATEMENT

Data are available on reasonable request.

ETHICS STATEMENT

None.

ORCID

Cihan Ay https://orcid.org/0000-0003-2607-9717
Johannes Oldenburg https://orcid.org/0000-0002-1585-4100

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ay C, Napolitano M, Hassoun A, et al. Classification of recombinant factor VIII products and implications for clinical practice: A systematic literature review. *Haemophilia*. 2024;1-12.
https://doi.org/10.1111/hae.15001