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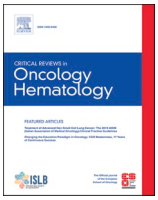

Clinical studies of extended-half-life recombinant FVIII products for prophylaxis in adults and children: A critical review from the physician's perspective

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ABSTRACT

This review compares the methodology of published clinical studies investigating the extended-half-life (EHL) factor VIII (FVIII) products, rFVIIIFc (efmoroctocog alfa, Elocta®/Eloctate®), BAY 94-9027 (damoctocog alfa pegol, Jivi®), BAX 855 (rurioctocog alfa pegol, Adynovate®) and N8-GP (turoctocog alfa pegol, Esperoct®) including the phase 2/3 studies, A-LONG (NCT01181128), PROTECT VIII (NCT01580293), PROLONG-ATE (NCT01736475) and pathfinder2 (NCT01480180), respectively, and their corresponding pediatric studies and extensions. Study results are interpreted from a treating physician's perspective, translating into evidence-based, real-life use of the different EHL recombinant FVIII products for personalized prophylaxis. The similarities between the studies include methodology, objectives, study design and cohort size. The differences include duration, prophylactic dosing intervals, number of patient arms, use of control group and randomization, and treatment allocation. Comparing these studies broadens physicians' understanding of each treatment's applicability. Further evaluation of study data and future real-world studies should help physicians to confidently individualize and select treatment for each patient.

1. Introduction

The development of new extended-half-life (EHL) recombinant factor VIII (rFVIII) products has the potential to significantly improve the level of care for patients with severe hemophilia A. EHL rFVIII products can be used to extend dosing intervals or to provide higher FVIII trough levels for longer periods (Jimenez-Yuste et al., 2014). It is expected that less frequent dosing may increase adherence, encourage patients to switch from on-demand treatment to prophylaxis, improve patient quality of life (QoL) by reducing the burden of frequent intravenous injections, and reduce the need for central venous lines (Jimenez-Yuste et al., 2014; Mancuso and Santagostino, 2017). Alternatively, maintaining increased trough levels, area under the concentration curve and time within the normal range may provide increased coverage for a more active lifestyle and help to prevent spontaneous breakthrough bleeding, leading to reductions in hemophilia-related complications (Jimenez-Yuste et al., 2014; Mancuso and Santagostino, 2017).

A variety of techniques have been developed to extend FVIII half-life, including PEGylation and Fc fusion. Four EHL rFVIII products that utilize these technologies have been recently approved: rFVIIIFc (efmoroctocog alfa, Elocta®/Eloctate®) (European Medicines Agency, 2020a), BAY 94-9027 (damoctocog alfa pegol, Jivi®) (European Medicines Agency, 2020b), BAX 855 (rurioctocog alfa pegol, Adynovate®) (European Medicines Agency, 2020c) and N8-GP (turoctocog alfa pegol, Esperoct®) (European Medicines Agency, 2020d). rFVIIIFc is an Fc fusion EHL rFVIII molecule, indicated for treatment and prophylaxis of bleeding in previously treated patients (PTPs) of all ages with hemophilia A, with a prophylactic regimen of 25–65 IU/kg every 3–5 days

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(E3–5D). BAY 94-9027, BAX 855 and N8-GP have all been PEGylated to extend their half-lives with 20 kDa, 40 kDa and 60 kDa PEG moieties, respectively, while rFVIIIFc uses Fc fusion technology. In the European Union, all four products are indicated for treatment and prophylaxis of bleeding events in PTPs aged >12 years with hemophilia A with the following prophylactic regimens: 40–50 IU/kg every 3–4 days (2×W, BAX 855), 50 IU/kg every 4 days (E4D, N8-GP) and a choice between 45 to 60 IU/kg every 5 days (E5D), 60 IU/kg every 7 days (E7D) and 30–40 IU/kg twice weekly (2×W) depending on the patient's individual bleeding profile and characteristics (BAY 94-9027). In the US, all have also been approved by the FDA for prophylactic and on-demand use in patients with hemophilia A aged <12 years, except for BAY 94-9027, which is not currently approved for use in pediatric patients (FDA, 2016; FDA, 2018; FDA, 2019a; FDA, 2019b).

Regulatory approval of these products was based on data from phase 2/3 clinical studies in selected PTP populations of different age groups (including children), using different study designs (e.g. randomization), treatment protocols and modalities (variable dosing regimens). Data are also available from extension studies of three EHL rFVIII products. However, there are limited published data or guidance available about how to use these products in routine clinical practice – typically obtained through phase 4, real-world studies. In routine clinical practice,

Table 1
Overview of key studies of EHL rFVIII products in adults/adolescents.

	A-LONG (NCT01181128) (Mahlangu et al., 2014)	**PROTECT VIII (NCT01580293)** (Reding et al., 2017)	**PROLONG-ATE (NCT01736475, NCT01599819)** (Konkle et al., 2015)	**pathfinder2 (NCT01480180)** (Giangrande et al., 2017)
Product	**rFVIIIFc (Eloctate®)**	**BAY 94-9027 (Jivi®)**	**BAX 855 (Adynovate®)**	**N8-GP (Esperoct®)**
Population				
Inclusion criteria	PTPs aged ≥12 years with severe hemophilia A treated prophylactically, or OD[a]	PTPs (≥150 EDs) aged 12–65 years with severe hemophilia A	PTPs (≥150 EDs) aged 12–65 years with severe hemophilia A	PTPs (≥150 EDs) aged 12–66 years with severe hemophilia A
Sample size[b]	165	134[c]	138[d]	186[e]
Design				
Design	Phase 3, open label, partially randomized	Phase 2/3, open label, partially randomized	Phase 2/3, open label, non-randomized	Phase 3, open label, non-randomized
Duration	6.4–12 months (± 2 weeks)	8.3 months (36 weeks)	≥50 EDs or 6 months ± 2 weeks	~19 months
Arm 1[f]	Individualized (i)PPX[g] 25–65 IU/kg E3–5D (n = 118)	2×W PPX 30–40 IU/kg, not eligible for randomization (NRnd) (n = 13)[h]	2×W PPX 45 ± 5 IU/kg (n = 121)	E4D PPX 50 IU/kg (n = 175)
Arm 2[f]	E7D PPX 65 IU/kg (n = 24)	2×W PPX 30–40 IU/kg, eligible for randomization (Rnd) (n = 11)[h]	OD 10–60 ± 5 IU/kg (n = 17)	OD (n = 12)
Arm 3[f]	OD 10–50 IU/kg (n = 23)	E5D PPX 45–60 IU/kg (n = 43)[h]		
Arm 4[f]		E7D PPX 60 IU/kg (n = 43)[h]		
Arm 5[f]		OD (n = 20)		
Basis for dose adjustment	Individual PK parameters	Bleeding rates[i]	NA	NA
Average infusion interval (mean)	3.9 days	5.2 days (Lalezari et al., 2019)	Not reported	4.1 days
Results				
Total ABR, median (Q1; Q3)	iPPX: 1.6 (0.0; 4.7) E7D PPX: 3.6 (1.9; 8.4) OD: 33.6 (21.1; 48.7)	2×W PPX, NRnd: 4.1 (2.0; 10.6) 2×W PPX, Rnd: 1.9 (0.0; 5.2) E5D PPX: 1.9 (0.0; 4.2) E7D PPX: 3.9 (0.0; 6.5) OD: 23.4 (17.8; 37.3) Total PPX (Bayer, 2020): 2.1 (0.0; 6.0)	2×W PPX: 1.9 (0.0; 5.8) OD: 41.5 (31.7; 51.1)	PPX: 1.3 (0.0; 4.6) OD: 30.9 (18.6; 38.5)
Safety				
All AEs	288 AEs reported in 108 (65.9%) patients	≥1 AEs reported in 100 (74.6%) patients	171 AEs reported in 73 (53.5%) patients	474 AEs reported in 145 (78%) patients
Treatment-related AEs	10 (6.1%) patients	12 (9%) patients	7 AEs in 6 patients	31 AEs (OD: 4; PPX: 27) in 18 patients
Inhibitors	None detected	None detected	None detected	Of 164 patients who received ≥50 EDs of N8-GP, one patient developed inhibitors against FVIII (≥0.6 BU)[j]

2×W: twice-weekly; ABR: annualized bleeding rate; AEs: adverse events; BU: Bethesda units; EDs: exposure days; EHL: extended-half-life; EXD: every X days; FVIII, factor VIII; iPPX: individualized prophylaxis; NA: not applicable; NRnd: not eligible for randomization; OD: on-demand; PK: pharmacokinetics; PPX: prophylaxis; PTPs: previously treated patients; Q: quartile; Rnd: eligible for randomization.

[a] With a history of ≥12 bleeding events in the 12 months prior to the study.
[b] Total number of patients assigned to treatment.
[c] Four patients withdrew from the study during the run-in period.
[d] Number of patients enrolled into each treatment arm.
[e] One patient changed treatment regimen from OD to prophylaxis and has been included in both prophylaxis and OD arms.
[f] Number of patients enrolled into each treatment arm.
[g] To maintain FVIII trough 1–3 IU/dL.
[h] 2×W prophylaxis (25 IU/kg) for 10-week run-in period.
[i] At patient's and investigator's discretion.
[j] Within the expected range of patients relative to the population size.

treatment decisions are influenced mainly by the bleeding phenotype and lifestyle, and so treatment is individualized. This is in contrast to clinical studies that are designed to evaluate outcomes such as the impact of different prespecified treatment regimens on bleeding phenotype or the maintenance of target trough levels within a desired range.

With the growing number of treatment options for patients with hemophilia, treatment decision-making is becoming more complex and requires careful consideration of benefits, risks and patient goals. This article summarizes the design of the phase 2/3 and phase 3 registration studies conducted with EHL rFVIII products in previously treated adult and pediatric hemophilia A populations. The primary aim of this article is to compare the methodology of the registration studies and interpret their results from the perspective of a treating physician. It also aims to explore which treatments and regimens may be most appropriate for different patient populations with specific characteristics (age, comorbidities etc.) and discuss how the comparison of registration studies can support treatment decision-making for a specific patient in clinical practice. Furthermore, the authors seek to identify gaps in knowledge and areas for further exploration.

2. Study methodology

2.1. Study design

Table 1–3 summarize the treatment arms of each study and the number of treated patients. All the studies were open label, as ethical considerations preclude blinded, placebo-controlled studies in hemophilia A. The main studies, their pediatric equivalents and their extensions, and the respective molecules they investigated comprise A-LONG (NCT01181128), Kids A-LONG (NCT01458106) and ASPIRE (NCT01454739) (rFVIIIFc); PROTECT VIII (NCT01580293), PROTECT VIII Kids (NCT01775618) and PROTECT VIII extension (BAY 94-9027); PROLONG-ATE (NCT01736475, NCT01599819) and PROLONG-ATE Kids (NCT02210091) (BAX 855); and pathfinder2 (NCT01480180), pathfinder5 (NCT01731600) and the pathfinder2 extension (NCT01480180) (N8-GP). All trials investigated their respective product as prophylaxis to prevent joint and spontaneous bleeding, as well as during and after minor surgeries. In each trial, additional infusions of the study treatment were available to all patients, if necessary, to treat bleeding episodes or to maintain hemostasis during minor surgeries. An on-demand arm was included for regulatory requirements in each main study on adults and adolescents, to either demonstrate efficacy for stopping a bleeding episode if necessary, or to act as a "control'' group to assess the extent of the improvements observed with prophylaxis patients.

A-LONG was a partially randomized study recruiting patients with previous prophylaxis or on-demand treatment who had the option to enter into Arm 1 (prophylaxis, 25–65 IU/kg rFVIIIFc E3–5D, individualized based on each patient's pharmacokinetic parameters) or be randomized into either Arm 2 (prophylaxis, 65 IU/kg rFVIIIFc E7D) or Arm 3 (on-demand, 10–50 IU/kg rFVIIIFc), with randomization based on individual bleeding episodes in the past 12 months (Mahlangu et al., 2014). All patients on a prophylactic regimen prior to study entry were enrolled into Arm 1. The prophylactic regimen for Arm 2 was designed to provide efficacy data to inform therapeutic decision-making for patients previously receiving on-demand treatment, who were unwilling or unable to undertake a more intensive protective regimen.

PROTECT VIII was also a partially randomized study in which patients entered a 10-week run-in period, receiving 25 IU/kg 2×W prophylaxis with BAY 94-9027. Patients with good bleed control (≤1 spontaneous breakthrough bleeds) during the run-in period were

Table 2
Overview of key studies of EHL rFVIII products in children.

	Kids A-LONG (NCT01458106) (Young et al., 2015)	PROTECT VIII Kids (NCT01775618) (Santagostino et al., 2020)	PROLONG-ATE Kids (NCT02210091) (Mullins et al., 2017)	pathfinder5 (NCT01731600) (Meunier et al., 2017)
Product	**rFVIIIFc (Eloctate®)**	**BAY 94-9027 (Jivi®)**	**BAX 855 (Adynovate®)**	**N8-GP (Esperoct®)**
Population – all studies included children <12 years old with severe hemophilia A				
Previous FVIII exposure	PTPs with ≥50 EDs	PTPs with >50 EDs	PTPs with ≥50 EDs if <6 y or ≥150 EDs if 6–<12 y	PTPs with >50 EDs if 0–5 y or >150 EDs if 6–11 y Body weight ≥10 kg
Sample size[a]	71	73	66	68
Design – all studies were phase 3, open-label, single-arm studies				
Duration	Up to 6 months (26 weeks)	≥50 EDs or 6 months	≥50 EDs or 6 months	~6 months (26 weeks)
Arm 1[b]	2×W PPX D1: 25 IU/kg; D4: 50 IU/kg[c]	1–2×W PPX (part 1) 2×W PPX 25–60 IU/kg	2×W PPX 50 ± 10 IU/kg	2×W PPX 50–75 IU/kg
Basis for dose adjustment	Individual PK parameters and bleeding patterns	NA, investigator selection	Individual PK parameters and bleeding patterns[d]	NA
Average dosing interval, median (IQR)	3.50 days (3.46–3.51)	Fixed	Not reported	Not reported
Results				
ABR, median (Q1; Q3)	2.0 (0.0; 4.0)	<6 y, part 1: 2.5 (1.2; 5.2) <6 y, part 2: 2.4 (0; 6.9) 6–12 y: 2.9 (0; 6.7)	2.0 (0.0; 3.9)	2.0 (0.0; 2.8)
All AEs	213 AEs reported in 59 (85.5%) patients	≥1 AEs reported in 61 (83.6%) patients	156 AEs reported in 43 (65.2%) patients	157 AEs reported in 50 (73.5%) patients
Treatment-related AEs	2 non-serious AEs	13 (17.8%) patients	Not reported	13 AEs in 10 patients
FVIII inhibitors	None detected	None detected	None detected	None detected

2×W: twice-weekly; ABR: annualized bleeding rate; AEs: adverse events; D: day; EDs: exposure days; EHL: extended-half-life; FVIII: factor VIII; IU: international units; IQR, interquartile range; NA: not applicable; PK: pharmacokinetics; PPX: prophylaxis; PTPs: previously treated patients; Q: quartile.

[a] Total number of patients assigned to treatment.

[b] Number of patients enrolled into Arm 1 equals the total number of patients assigned to treatment.

[c] Dose and dosing interval were adjusted based on PK and bleeding tendency.

[d] At the investigator's discretion.

Table 3
Overview of key extension studies of EHL rFVIII products.

	ASPIRE (NCT01454739) (Nolan et al., 2020)			PROTECT VIII extension (Lalezari et al., 2019)	PROTECT VIII Kids extension (Kenet et al., 2018)	pathfinder2 extension (NCT01480180) (Curry et al., 2019)
Product	**rFVIIIFc (Eloctate®)**			**BAY 94-9027 (Jivi®)**	**BAY 94-9027 (Jivi®)**	**N8-GP (Esperoct®)**
Population						
Inclusion criteria	Patients who completed A-LONG or Kids A-LONG			Patients who completed PROTECT VIII	Patients who completed ≥50 EDs and ≥6 months in PROTECT VIII Kids or the 12-week safety part 2 of the study	Patients who completed pathfinder 2 with ≤ 2 bleeds during the preceding 6 months of the main study and willing to undergo randomization
Sample size[a]	211			121	59	143
Design						
Design	Phase 3, open label Non-randomized			Open-label extension Non-randomized		Two-part extension Randomized and non-randomized cohorts
Duration	~60 months (5 years)			Up to 74 months (6.2 years) (Holme et al., 2020)	Additional ≥50 EDs	Part 1: 5.5 months (24 weeks)
Extension	***A-LONG patients***	***Kids A-LONG patients***		***PROTECT VIII***	***PROTECT VIII Kids***	***pathfinder2***
		<6 years	***6–12 years***			
Arm 1[b]	Individualized (i) PPX[c] (n = 110)	iPPX[c] (n = 29)	iPPX[c] (n = 30)	2×W PPX 30–40 IU/kg (n = 23)	2×W PPX 25 IU/kg (n = 20)	E4D PPX 50 IU/kg (n = 17)
Arm 2[b]	E7D PPX 65 IU/kg (n = 27)			E5D PPX 45–60 IU/kg (n = 33)	E5D PPX 45 IU/kg (n = 21)	E7D PPX 75 IU/kg (n = 38)
Arm 3[b]	Modified (m)PPX[d] (n = 21)	mPPX[d] (n = 2)	mPPX[d] (n = 1)	E7D PPX 60 IU/kg (n = 23)	E7D PPX 60 IU/kg (n = 8)	E4D 50 IU/kg non-randomized (n = 88)
Arm 4[b]	OD (n = 13)			VAR[e] (n = 28)	VAR (n = 10)	
Arm 5[b]				OD (n = 14)		
Basis for dose adjustment	NA	NA	NA	Bleeding patterns		NA
Average dosing interval, median (IQR)	iPPX: 3.5 (3.5–5.0) E7D: 7.0 (7.0–7.1) mPPX: 5.0 (4.0–6.9)	iPPX: 3.5 (3.5–3.5)	iPPX: 3.5 (3.5–3.5)	All PPX: 5.0 (IQR not reported)	Not reported	Not reported
Results						
Total ABR, median (Q1; Q3)	iPPX: 0.7 (0.0; 2.7) E7D: 2.2 (0.4; 5.1) mPPX: 4.1 (1.2; 8.8) OD: 19.1 (15.1; 0.5)	iPPX: 1.2 (0.6; 2.4)	iPPX: 1.6 (0.6; 3.6)	Total PPX: 1.6 (0.3; 4.6) 2×W: 1.7 (NR) E5D: 1.2 (NR) E7D: 0.7 (0; 1.6) VAR: 3.1 (1.2; 6.2) OD: 34.1 (20.3; 36.6)	Total PPX: 1.7 (NR) 2×W: 1.0 (NR) E5D: 1.2 (NR) E7D: 2.6 (NR) VAR: 3.3 (NR)	E4D: 0.0 (0.0–2.2) E7D: 0.0 (0.0–2.4)
All AEs	≥1 AE reported in 184 (87.2%) patients	≥1 AE reported in 55 (90.2%) patients		NR	NR	108 AEs reported in 36 (65.5%) patients
Treatment related AEs	3 AEs in 2 patients	NR		**During the extension** All PPX: 9 (7.4%) patients	Four patients (6.8%) experienced treatment related AEs; two patients (3.4%) experienced treatment related SAEs (Ahuja et al., 2020)	All arms: 5 AEs in 5 patients
FVIII inhibitors	None detected	None detected	None detected	None detected	None detected	None detected

2×W: twice-weekly; ABR: annualized bleeding rate; AEs: adverse events; EHL: extended-half-life; EXD: every X days; FVIII: factor VIII; iPPX: individualized prophylaxis; IU: international units; mPPX; modified prophylaxis; NA: not applicable; NR: not reported; OD: on-demand; PPX: prophylaxis; Q: quartile; SAEs: serious adverse events; VAR: variable frequency.

[a] Total number of patients assigned to treatment.

[b] Number of patients enrolled into each treatment arm.

[c] 25–65 IU/kg rFVIIIFc E3–5D, or 2×W rFVIIIFc (Day 1: 20–65 IU/kg; Day 4: 40–65 IU/kg).

[d] Dosing could be adjusted to meet the needs of individual patients; this included, but was not limited to, less frequent dosing, addition of 'prevention' doses prior to strenuous activity, or targeting a FVIII trough level of >3% (if the bleeding history and/or activity level required).

[e] Patients who switched PPX regimen during the extension were analyzed in the variable frequency group.

randomized 1:1 to receive prophylaxis with 45–60 IU/kg E5D or with a fixed dose of 60 IU/kg E7D until these arms were full (capped at 43 patients) (Reding et al., 2017). This individualized study design allowed patients who demonstrated good bleed control on 2×W prophylaxis to adjust their dosing schedule to longer intervals between infusions.

PROLONG-ATE was a non-randomized study in which patients were assigned to treatment regimens of BAX 855 based on their prestudy treatment: patients who received prophylaxis previously were assigned to the prophylaxis group; the first 17 patients who were previously treated on-demand were assigned to the on-demand group; and

additional on-demand patients were assigned to the prophylaxis arm. Patients in the prophylaxis arm received 45 ± 5 IU/kg 2×W, designed to ensure maintenance of FVIII levels over 1% (Konkle et al., 2015).

Pathfinder2 was also a non-randomized study, investigating N8-GP, in which patients received either prophylaxis (50 IU/kg E4D) or doses of 20–70 IU/kg on-demand (Giangrande et al., 2017). Patients in the prophylaxis arm could switch to 2×W dosing at the discretion of the investigator.

The clinical trial programs included studies conducted in pediatric PTPs (≥50 exposure days [EDs]) with hemophilia A, investigating prophylaxis with the respective EHL rFVIII product in children. Kids A-LONG (rFVIIIFc), PROTECT VIII Kids (BAY 94-9027), PROLONG-ATE Kids (BAX 855) and pathfinder5 (N8-GP) were all open-label, single-arm studies in previously treated children aged ≤ 12 years. In Kids A-LONG, patients were treated 2×W with 25 IU/kg on Day 1 and 50 IU/kg on Day 4, with adjustments in dose (up to 80 IU/kg) and interval (minimum of every 2 days [E2D]) allowed (Young et al., 2015). During part 1 of PROTECT VIII Kids, patients started at 25 IU/kg 2×W, 45 IU/kg E5D, or 60 IU/kg E7D BAY 94-9027 depending on the investigators' judgement (Santagostino et al., 2020) and could switch regimen at any time. In part 2, 12 additional children <6 years of age were enrolled and given 25–60 IU/kg BAY 94-9027 2×W for 12 weeks in order to obtain further safety data, which were needed due to a higher-than-expected withdrawal rate among patients aged <6 years in part 1. In PROLONG-ATE Kids, patients received 50 ± 10 IU/kg 2×W BAX 855 with dose increases of up to 80 IU/kg allowed according to predefined criteria (Mullins et al., 2017). In pathfinder5, patients received 60 (50−75) IU/kg 2×W N8-GP with increases in dosing frequency to E3D permitted by the investigator, depending on bleeding patterns (Meunier et al., 2017). In all pediatric studies, patients were analyzed by age group: <6 years and 6–11 or 6–<12 years.

Four studies, A-LONG, PROTECT VIII, PROTECT VIII Kids and pathfinder2, had further extension studies to evaluate long-term efficacy and safety in patients who completed the phase 2/3 main study periods and agreed to remain in the extension phase. Patients could enter ASPIRE upon completion of A-LONG or Kids A-LONG. A-LONG patients were treated with one of three prophylactic regimens (individualized, weekly, modified) or on-demand. Kids A-LONG patients were treated with either individualized or modified prophylaxis regimens (Nolan et al., 2020). Patients could enter the PROTECT VIII/PROTECT VIII Kids extension studies upon completion of the PROTECT VIII and PROTECT VIII Kids main studies, in which they could receive any prophylaxis regimen used in the main study (30–40 IU/kg 2×W, 45–60 IU/kg E5D, or 60 IU/kg E7D BAY 94-9027) or continue with on-demand treatment (Kenet et al., 2018; Lalezari et al., 2019; Reding et al., 2018). Patients could enter Part 1 of the pathfinder2 extension upon completion of the pathfinder2 main study, in which those who experienced ≤ 2 bleeds during the preceding six months were randomized to receive either 50 IU/kg E4D or 75 IU/kg E7D N8-GP; those who did not meet the randomization criteria received 50 IU/kg E4D (Curry et al., 2019).

The duration of the main studies in adolescents and adults varied from ≥50 EDs or from 6 months ± 2 weeks to 21.6 months (1.8 years) (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017), and up to 6 months (≥50 EDs or 26 weeks) in all pediatric main studies (Young et al., 2015; Mullins et al., 2017; Meunier et al., 2017). The duration of both the ASPIRE and PROTECT VIII extension studies was approximately 60 months (5 years) (Nolan et al., 2020; Lalezari et al., 2019; Reding et al., 2018). Part 1 of the two-part pathfinder2 extension was 5.5 months (24 weeks) (Curry et al., 2019).

Notably, the study design has evolved along with our understanding of EHL rFVIII products. A-LONG, published in 2014, aimed to maintain FVIII trough levels above 1–3%, which was an advancement from the typical aim of standard-half-life (SHL) products to maintain trough levels above 1%. However, as clinical experience with EHL rFVIII products amassed, the approach to study design has evolved, whereby different studies are exploring different outcomes. This allows for the exploration of the flexibility and range of therapeutic options of each molecule. For example, with PROTECT VIII, published in 2017, the focus of the study design shifted from achieving specific trough levels to identifying patients who were best suited for extended interval dosing, reflecting an improved understanding of what was and was not possible with EHL rFVIII products.

2.2. Patient inclusion and exclusion criteria

Key inclusion and exclusion criteria were similar in the four main clinical studies in adolescents and adults (aged ≥12–65 or 66 years). They all included PTPs (≥150 EDs, not specified in A-LONG) with severe hemophilia A (<1 IU/dL [1%] endogenous FVIII levels) and no history of FVIII inhibitors.

Likewise, key inclusion and exclusion criteria were similar in the four clinical studies in children (aged <12 or ≤12 years) (Young et al., 2015; Santagostino et al., 2020; Mullins et al., 2017; Meunier et al., 2017). They all included PTPs with severe hemophilia (<1 IU/dL [1%] FVIII) and no history of FVIII inhibitors. Kids A-LONG included patients with ≥50 EDs, PROTECT VIII Kids included patients with >50 EDs, PROLONG-ATE Kids included patients with ≥50 EDs if aged <6 years and ≥150 EDs if aged 6–<12 years, and pathfinder5 included patients with >50 EDs if aged 0–5 years and >150 EDs if aged 6–11 years and body weight ≥10 kg.

For the extension studies, the key inclusion criterion was successful completion of the main study (PROTECT VIII and Kids extension and pathfinder2 extension). For ASPIRE, both adult and adolescent patients who successfully completed A-LONG and pediatric patients who completed Kids A-LONG were eligible for enrollment.

2.3. Outcome measures

Annualized bleeding rate (ABR), defined across the pivotal studies as the total number of bleeds per year experienced by the patients in each treatment regimen during the study period, is the primary or co-primary efficacy outcome for each pivotal study analyzed in this review (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017; Young et al., 2015; Santagostino et al., 2020; Mullins et al., 2017; Meunier et al., 2017; Nolan et al., 2020; Kenet et al., 2018; Lalezari et al., 2019; Curry et al., 2019). All studies also investigated the number of injections and dose per injection required to resolve a bleed. FVIII activity (treatment-induced FVIII trough levels) was assessed using one-stage assay, chromogenic assay, or both, as the primary outcome in A-LONG, and as a secondary outcome in: Kids A-LONG; PROTECT VIII and PROTECT VIII Kids; PROLONG-ATE and PROLONG-ATE Kids; and pathfinder5 (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Young et al., 2015; Santagostino et al., 2020; Mullins et al., 2017; Meunier et al., 2017). For the main studies in adults that evaluated FVIII activity using both one-stage and chromogenic assays, measurements were similar between the assays (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017). Other pharmacokinetic (PK) parameters were assessed in all main studies for all ages. For PROTECT VIII, PROLONG-ATE, and pathfinder2, area under the concentration curve, terminal half-life, clearance, and volume of distribution were among a variety of PK parameters that were taken at regular intervals from pre-injection until up to 96 h following the administration of the study drug at baseline and at the end of the study (Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017). For A-LONG, however, they were taken at regular intervals from pre-injection up to 120 h following the administration of the study drug at baseline, and then at Weeks 12 and 24 (Mahlangu et al., 2014). Although the main pivotal studies varied in terms of statistical software used, descriptive statistics used across them included median and interquartile range ABR values for each treatment arm, and a negative binomial regression model was most commonly used to make intergroup comparisons. Various studies reported a selection of patient-reported outcomes

(PROs). Patients' assessment of response to treatment of bleeds was evaluated in PROTECT VIII, PROTECT VIII extension, Kids A-LONG and ASPIRE (Reding et al., 2017; Young et al., 2015; Nolan et al., 2020; Lalezari et al., 2019), while the four-point hemostatic efficacy rating was assessed in PROTECT VIII Kids, ASPIRE and the BAX 855 and N8-GP studies (Konkle et al., 2015; Giangrande et al., 2017; Santagostino et al., 2020; Mullins et al., 2017; Meunier et al., 2017; Nolan et al., 2020). The Hemo-SYM questionnaire and 36-item Short Form survey were both only assessed in PROLONG-ATE (Konkle et al., 2015); Pediatric Quality of Life Inventory™, pain visual analogue scale, and Physical Activity Questionnnaire were only assessed in PROLONG-ATE Kids (Mullins et al., 2017). A-LONG and PROTECT VIII Kids extension omitted collection of PROs (Mahlangu et al., 2014; Kenet et al., 2018).

The incidence of FVIII inhibitors (immunogenicity) and adverse events were the key safety outcomes across all studies, while other safety outcomes (medical events of special interest, non-neutralizing antibodies, vital signs and laboratory parameters) were also measured at various time points across the different studies.

3. Baseline characteristics

Generally, interpatient variation was small within the four clinical studies in adolescents and adults (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017). Most participants were white (65–75%), with an average weight of 72–75 kg. Of note, PROTECT VIII and pathfinder2 report mean values for age (35.9 and 31.1 years, respectively), while A-LONG and PROLONG-ATE report median values (30 and 29 years, respectively). Similarly, interpatient variation was small within the three clinical studies in children (Young et al., 2015; Santagostino et al., 2020; Mullins et al., 2017; Meunier et al., 2017).

People living with HIV were included in all adult and adolescent studies except PROLONG-ATE, and the proportion of patients with HIV ranged from 7% to 22%. In pathfinder2, patients with HIV with a viral load >400,000 copies/ml were excluded. Patients with hepatitis C (HCV) were included in all studies and made up 30–58% of each population (Mahlangu et al., 2014; Reding et al., 2017; Konkle et al., 2015; Giangrande et al., 2017).

Most adult and adolescent patients (68–73%) had target joint(s) at baseline, whereas in the pediatric studies, only approximately one-fifth (18–22%) of patients had target joint(s) at baseline (Table 4). Pre-study median (Q1; Q3) ABR in A-LONG was 6.0 (2; 15) and 27.0 (18; 40) for patients who were treated with prophylaxis or on-demand in the 12 months prior to study, respectively (Mahlangu et al., 2014). Median ABR (Q1; Q3) in patients treated prophylactically and episodically 12 months prior to enrollment in pathfinder2 was 2.0 (1; 8) and 30 (12; 52), respectively (Giangrande et al., 2017). Mean (standard deviation [SD]) ABR 12 months prior to PROTECT VIII for all patients was 15.3 (18.6) and patients treated with prophylaxis had a mean (SD) ABR ranging from 8.1 (11.8; E7D) to 28.7 (32.4; 2×W, eligible for randomization); patients treated on-demand during this period had a mean (SD) ABR of 27.9 (17.8) (Reding et al., 2017). No prestudy bleeding data are published for PROLONG-ATE, PROLONG-ATE Kids, or pathfinder5 (Konkle et al., 2015; Mullins et al., 2017; Meunier et al., 2017). Type of FVIII treatment prior to study enrollment is reported in Table 4.

Although limited, baseline patient demographic data for the ASPIRE, PROTECT VIII extension and pathfinder2 extension studies are assumed to be similar to those of the main studies, as they largely involved the same patients. Mean (SD) age of patients in the pathfinder2 extension study was 29.5 (13.9) years, with mean (SD) weight of 78.2 (15.6) kg. Median (range) age of patients in the ASPIRE and PROTECT VIII extension studies was 20 (2−66) years and 36 (12−62) years, respectively. Weight was not reported for ASPIRE or PROTECT VIII extension, although median (range) body mass index of 24.0 (15−42) kg/m^2 was reported for the PROTECT VIII extension study (Table 4).

4. Efficacy and safety results

Key efficacy and safety results for each study are summarized in Table 1–3. As expected, prophylaxis with all EHL rFVIII products resulted in lower median ABRs as compared with on-demand treatment. In particular, patients in the individualized prophylaxis arm of A-LONG had a lower median ABR (1.6) compared with patients in the fixed E7D prophylaxis arm (3.6). In PROTECT VIII, median ABRs for patients randomized to different prophylactic regimens ranged from 1.9 (E5D) to 3.9 (E7D). During the four clinical studies in adolescents and adults, only one patient developed FVIII inhibitors during treatment with an EHL rFVIII (N8-GP, pathfinder2), which was within the expected range for PTPs of this sample size; no incidences of FVIII inhibitors were observed in the other three studies. During the four clinical studies in pediatric PTPs, no patients developed FVIII inhibitors.

5. Discussion

To our knowledge, this review is the first to evaluate the study design and data from different clinical studies assessing EHL rFVIII as prophylaxis in children and adults from a treating physician's perspective. In total, 900 pediatric, adolescent and adult patients were assessed in eight pivotal clinical studies evaluating four EHL rFVIII products. This informative exercise highlighted the similarities between these studies, such as methodology, objective, study design (use of randomization and specific inclusion criteria), and cohort size. However, there are also major differences between the studies which, together with a lack of head-to-head comparisons of the products as well as a lack of formal network meta-analysis, means that the studies cannot be compared directly.

One such difference is the main study and extension durations. For example, the PROTECT VIII main study primary endpoint was 8.3 months (36 weeks) with an extension period of up to >60 months (5 years) (Lalezari et al., 2019), whereas the pathfinder2 main study primary endpoint was approximately 19 months, with an extension period of a further 5.5 months (24 weeks) in Part 1 (Curry et al., 2019) (Table 1). Other notable differences include prophylaxis dosing intervals, number of treatment arms and use of a control group, as well as the use of randomization and treatment allocation. For instance, in A-LONG, randomization was based on individual PK parameters, whereas in PROTECT VIII, randomization to extended dosing intervals of every 5 or 7 days was based on baseline bleeding phenotype, determined during a 10-week run-in period where all participants were treated with the same 2×W dosing (Mahlangu et al., 2014; Reding et al., 2017). Dose adjustments made during the studies could be based on trough levels and bleeding rates (A-LONG (Mahlangu et al., 2014) and PROTECT VIII (Reding et al., 2017), respectively), pre-study FVIII regimen (PROLONG-ATE) (Konkle et al., 2015), or PK data from a previous study (pathfinder2) (Giangrande et al., 2017). There were also differences in the bleeding phenotype and medical history of patients at enrollment. The total estimated number of bleeding events in the 12 months prior to the study in patients who received prophylaxis ranged from a median (Q1; Q3) of 2.0 (1.0; 8.0) (Giangrande et al., 2017), through 6.0 (2.0; 15.0) (Mahlangu et al., 2014) or to a mean (± SD) ranging from 8.1 (± 11.8) to 28.7 (± 32.4) (Reding et al., 2017) depending on the dosing regimen.

For all prophylaxis regimens investigated in the four clinical studies in adults and adolescents, the vast majority of patients (92.2%) successfully completed their respective main study phase, ranging from 89.7% (E4D prophylaxis in pathfinder2) to 97.7% (E5D prophylaxis in PROTECT VIII) among those receiving prophylaxis.

Interim data from the extension phases of these four studies suggest that the efficacy of rFVIIIFc, BAY 94-9027 and N8-GP is maintained for up to five years (Nolan et al., 2020; Kenet et al., 2018; Lalezari et al., 2019; Curry et al., 2019). These studies demonstrate consistently the efficacy of EHL rFVIII products used as prophylaxis at various infusion

Table 4
Baseline patient demographics and disease characteristics.

Study	Adult/adolescent				Children				Extension studies			
	A-LONG (Mahlangu et al., 2014**)**	**PROTECT VIII (** Reding et al., 2017; Ducore et al., 2019**)**	**PROLONG-ATE (** Konkle et al., 2015**)**	**pathfinder2 (**Giangrande et al., 2017**)**	**Kids A-LONG (**Young et al., 2015**)**	**PROTECT VIII Kids (** Santagostino et al., 2020**)**	**PROLONG-ATE Kids (** Mullins et al., 2017**)**	**pathfinder5 (**Meunier et al., 2017**)**	**ASPIRE (**Nolan et al., 2020**)**	**PROTECT VIII extension (**Lalezari et al., 2019**)**	**PROTECT VIII Kids extension (**Kenet et al., 2018**)**	**pathfinder2 extension (** Curry et al., 2019**)**
N	165	134[a]	137	186[b]	71	73	66	68	211	121	59	55
BMI, kg/m^2												
Mean (SD) Median (range)		24.7 (4.7)					17.1 (2.9)			24.0 (15–42)		25.2 (4.2)
						Part 1: *<6 y:* 15.5 (13–18) *6–<12 y:* 16.4 (13–22) Part 2: 15.3 (14–17)						
Race, %												
White	64.8	65.7	75.2	74.2	67.6	Part 1: 90.2 Part 2: 83.3	80.9	65.2	74.4[c]	64.5		87.3
Black/African American	6.1	3.7	0.7	5.9	12.7	Part 1: 4.9 Part 2: 0	4.4	6.1	4.8[c]	4.1		1.8
Asian	26.1	23.9	24.1	18.8	7.0	Part 1: 3.3 Part 2: 8.3	7.4	25.8	16.6[c]	24.8		10.9
Other[d]	3.0	6.7	0.0	1.1	12.7	Part 1: 1.6 Part 2: 8.3	7.4	3.0	4.1[c]	6.6		
Target joints												
Patients with target joints, %	Prior PPX: 47 (28.5) Prior OD: 66 (40.0)	73.1[e]	67.9		18.3	Part 1: 18 Part 2: 0	22.1	21.2		PPX: 72.0 OD: 78.5		
Previous treatment												
PPX (n)	87	89	120	175	8	Part 1: 56 **Part 2:** 12	61	65				
OD (n)	78	43	17	12	63	Part 1: 5 **Part 2:** 0	5	3				

BMI: body mass index; OD: on-demand; PPX: prophylaxis; Q: Quarter; SD: standard deviation.
[a] Previous treatment is unknown for two patients.
[b] One patient changed treatment regimen from OD to prophylaxis and has been included in both prophylaxis and OD arms.
[c] Median value has been calculated from values across different patient arms.
[d] Not reported/multiple.
[e] Mean (SD) of 1.7 (1.6) target joints per patient.

intervals. This potential to prolong the time between infusions enables treatment individualization, but the extent of prolongation of infusions varies between products and between patients, owing to their individual bleeding phenotypes and lifestyle. As such, not all patients can be treated the same way and so treatment individualization is of major importance. FVIII trough levels still have an important role in dose adjustment, however, there is evidence to suggest that the attainment of FVIII trough levels of 1–3 IU/dL, previously considered the main treatment goal, is insufficient to completely prevent bleeds in all patients with hemophilia and can lead to hemophilic arthropathy over a patient's lifespan (Srivastava et al., 2020). Therefore, the current treatment goal of EHL rFVIII prophylaxis is to fully support patients' social and physical activities by maintaining higher trough levels (over 3–5%, or higher) without increasing the number of infusions (Srivastava et al., 2020). At the same time, the studies also demonstrated that some patients do not bleed, despite short periods with trough levels below 1%. The studies on EHL rFVIII products discussed in this review provide a limited insight into how effectively the different EHL rFVIII products maintain FVIII trough levels at a steady state during regular prophylaxis. Certain studies, namely PROTECT VIII and A-LONG together with their corresponding pediatric studies and extensions, enabled treatment individualization by allowing for varying prophylaxis intervals, provided that the patient and investigator both agreed that the patient had achieved adequate bleeding control. This approach demonstrated that BAY 94-9027 prophylaxis regimens can be adjusted to best fit the needs of each patient. However, the studies analyzed here did not help to identify the ideal patient demographics, treatment history, joint status and bleeding characteristics required to establish which patient type is most suitable for which regimen at baseline. They also do not help to identify the characteristics of patients who can be allocated to a specific treatment regimen.

Another factor that limits treatment individualization is the lack of real-world data to help produce algorithms that can identify the most suitable product and treatment regimen for each patient. Real-world data are useful because, problematically, patient characteristics in registration studies may not be fully representative of patients who receive these products in clinical practice. There is also a lack of data in patients with a history of inhibitors, or those who have been tolerized. Patients with a previous history of inhibitors are excluded from these pivotal trials, regardless of achieving tolerance. Such patients could account for a significant proportion of the hemophilia A population, considering that approximately 30% develop inhibitors after first exposure in childhood, and 70% of those are successfully or partially tolerized (Meeks and Batsuli, 2016). Additionally, there are few published clinical data and limited evidence on the use of EHL rFVIII products in immune tolerance induction, although available evidence is favorable towards using EHL rFVIII for this purpose and warrants further exploration (Janbain and Pipe, 2016; Lambert et al., 2018). Well-designed, long-term extension studies can reflect real-world treatment settings better and address the gaps, such as long-term outcomes of prophylaxis treatment, and real-world data can address the gap of the exclusion of patients with a history of inhibitors. During the PROTECT VIII extension, for example, patients had relatively few study visits during more than 6 years of observation, which allowed the treating physicians and patients the freedom to switch treatment regimens with no restrictions, adjusting them to the patient's lifestyle.

This review has some limitations. For example, we were unable to make direct inter-study comparisons or conduct a meta-analysis because of differing study designs and populations. A limitation inherent to any indirect comparison of studies is that it is often affected by relatively small numbers of patients and variability between study populations. There is a lack of head-to-head efficacy and safety data as the studies did not compare treatments with different products and, to date, only two head-to-head crossover PK studies comparing EHL rFVIII products have been published (Shah et al., 2019; Solms et al., 2020). Improvements in several PK parameters (half-life, clearance and area under the concentration curve) following a single infusion of BAY 94-9027 compared with a single infusion of rFVIIIFc have been reported (Shah et al., 2019), while a similar study comparing the PK of two PEGylated EHL rFVIII products also reported PK improvements following a single infusion of BAY 94-9027 compared with a single infusion of BAX 855 (Solms et al., 2020). A Canadian non-crossover real-world study reported almost identical PK profiles of BAX 855 and rFVIIIFc in 25 adolescents aged 12–18 years who switched from rFVIIIFc to BAX 855 (Carcao et al., 2019).

Additionally, there is a lack of data on the use of EHL rFVIII to treat breakthrough bleeds for non-inhibitor patients treated with non-factor replacement therapies. Emicizumab (Hemlibra®) is the first licensed non-factor replacement therapy for hemophilia A and currently, there are no published data on the efficacy of EHL rFVIII when used to treat bleeds in patients treated prophylactically with emicizumab.

Lastly, shared decision-making needs to be considered in the context of hemophilia clinical studies and treatment individualization. Patients should be educated about the treatment, its risk, availability, benefits and costs, to feel confident discussing their preferences with their healthcare professional (Nossair and Thornburg, 2018). Likewise, in order to support the patient, the healthcare professional should be educated on the available evidence regarding efficacy, safety, dosing and monitoring strategies. Adequately informed patients and healthcare professionals are best prepared to make decisions about the treatment together, ultimately devising a care plan that can effectively support the patient.

Each of the studies discussed here, whether the initial dosing regimen was decided based on PK, bleeding rates or prior FVIII treatment, aimed to assess efficacy and safety of their respective EHL rFVIII treatments in patients with hemophilia A. Comparing the methodologies of the EHL rFVIII studies discussed here, together with their pediatric branches and extensions, allows for a better understanding of the clinical application of each treatment. Furthermore, from a physician's perspective, comparing the methodologies and results of the studies on EHL rFVIII products outlined in this review could be of value when selecting treatment for a given patient and can enhance treatment decision-making. Further evaluation of these registration studies may be able to impact clinical practice by supporting clinicians in assessing the suitability of specific treatments and dosing regimens for specific patients. Future investigations should collect real-world data from large groups of patients treated with EHL rFVIII product regimens, which may help with treatment individualization in order to provide a better understanding of the right treatment for the right patient.

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Cedric Hermans contributed to the design, critically reviewed and approved the manuscript for submission. Mark T Reding, Jan Astermark, Robert Klamroth, and Maria Elisa Mancuso all critically reviewed and approved the manuscript for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial

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