









## SYSTEMATIC REVIEW

# REVISED Efficacy, safety, and immunogenicity of rurioctocog alfa pegol for prophylactic treatment in previously treated patients with severe hemophilia A: a systematic review and meta-analysis of clinical trials [version 3; peer review: 2 approved]

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## Abstract

**Background:** Patients with severe hemophilia often present with painful joint and soft tissue bleeding which may restrict them from their daily activities. The current standard of care still relies on a regular prophylactic factor VIII (FVIII), which has a high daily treatment burden. Recently, rurioctocog alfa pegol, a third-generation recombinant FVIII with a modification in its polyethylene glycol (PEG) component, has been developed. Several trials have studied this synthetic drug as bleeding prophylaxis in severe hemophilia A. This study aims to evaluate the efficacy, safety, and immunogenicity of rurioctocog alfa pegol for previously treated patients with severe hemophilia A.






**Methods:** This study was conducted in conformity with the PRISMA guidelines. Data were retrieved from PubMed, Scopus, Cochrane Library, Wiley Online Library, and CINAHL (via EBSCOhost). Study qualities were assessed using the Methodological Index for Non-Randomized Studies (MINORS) and Modified Jadad scales.


**Results:** Four studies involving 517 previously treated severe

## Open Peer Review

Reviewer Status  

Invited Reviewers

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hemophilia A patients were included in this study. The pooled mean of total annualized bleeding rate (ABR) and hemostatic efficacy was 2.59 (95% CI = 2.04–3.14) and 92% (95% CI = 85%–97%), respectively. Only 30 (2.3%) non-serious and one (1.4%) serious adverse events were considered related to rurioctocog alfa pegol treatment. At the end of the studies, no development of FVIII inhibitory antibodies was observed. None of the developed binding antibodies to FVIII, PEG-FVIII, or PEG was correlated to the treatment efficacy and safety.

**Conclusions:** Despite the limited availability of direct comparison studies, our analyses indicate that rurioctocog alfa pegol could serve as a safe and effective alternative for bleeding prophylaxis in previously treated hemophilia A patients. Moreover, it appears to have low immunogenicity, which further increases the safety profile of the drug in such clinical conditions.

### Keywords

drug safety, efficacy, hemophilia A, human and medicine, immunogenicity, prophylaxis, rurioctocog alfa pegol

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Any reports and responses or comments on the article can be found at the end of the article.

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**REVISED Amendments from Version 2**

We have removed unnecessary information to shorten the introduction to hemophilia and added additional information regarding the importance, burden, and theoretical importance of extended half-life rFVIII in the introduction section. We have revised the numbering of the references to the correct order. We have added more contents for the discussion and we have added Egger's test in the result section.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Hemophilia A is a rare, X-linked recessive, congenital bleeding disorder caused by mutations or defects in the factor VIII (FVIII)-producing genes.<sup>1</sup> Those mutations manifest as a congenitally absence or decrease of the FVIII, an important pro-coagulant cofactor in the bleeding hemostasis.<sup>2</sup> Hemophilia A may be further classified into mild, moderate, and severe based on the FVIII levels.<sup>1</sup> The severe form of hemophilia A is defined as having FVIII levels <1% of normal, while the mild and moderate forms have higher FVIII levels that are approximately 5–50% and 1–5%, respectively.<sup>3</sup> Patients with severe hemophilia often present with internal bleeding, especially in the joints and soft tissues. Joint and soft tissue bleeding, along with painful feelings, may restrict patients from their daily activities due to the restriction on their range of motions.<sup>3,4</sup> If this bleeding continues without being treated adequately, hemophilic patients could suffer from more advanced complications, including hemophilic arthropathy. This is important since hemophilic arthropathy could negatively affect their quality of life due to the severe joint immobility.<sup>3</sup>

The current management of hemophilia A relies on two options: (1) episodic or on-demand FVIII replacement if the patients present with any bleedings to prevent further bleeding or (2) prophylactic FVIII treatment to maintain the FVIII levels and prevent any future bleedings.<sup>5</sup> However, the first option was no longer recommended as primary long-term management due to no alteration found in its natural disease course.<sup>6</sup> To date, the standard of care for hemophilia A, especially the severe form, still relies on a regular prophylactic intravenous FVIII replacement therapy.<sup>3</sup> The standard prophylactic regimens have shown a positive effect in reducing the future joint disease in hemophilia A. However, their half-lives are considered short, approximately 8–12 h, which will eventually increase the administration frequency.<sup>4</sup> Additionally, more than 30% of patients with hemophilia A may develop 'inhibitors' or refer to as neutralizing anti-drug antibodies to the standard prophylactic treatment which has high immunogenicity in inducing its formation.<sup>3</sup> Thus, extended half-life and safer prophylactic agents may be beneficial in reducing the daily treatment burden, and at the same time, those agents could maintain better clinical presentations and improve the treatment efficacy.<sup>7</sup>

Recently, rurioctocog alfa pegol (i.e., BAX 855), a third-generation recombinant FVIII (rFVIII) with a modification in its polyethylene glycol (PEG) component, has been developed. The addition of PEG in rFVIII or referred to as PEGylation is addressed to decrease its plasma clearance and to alter its biodistribution in the human body.<sup>8</sup> This modification also prolongs the half-life of rFVIII by 1.4–1.5 folds the original rFVIII, thereby reducing the administration frequency and maintaining better bleeding hemostasis of the hemophilic patients.<sup>8,9</sup> The administration of rurioctocog alfa pegol increases the prevalence of zero-bleeding events in hemophilia A patients due to its lower future coagulation factor consumption after injection compared to the standard regimens. Hence, the use of this drug could offer potential advantages and might improve treatment adherence.<sup>8</sup> Yet, to the best of our knowledge, there are no pooled studies assessing the efficacy, safety, and immunogenicity of rurioctocog alfa pegol as a prophylactic treatment. Therefore, here, we aim to evaluate the efficacy, safety, and immunogenicity of rurioctocog alfa pegol, a newly-developed prophylactic agent, in previously treated patients with severe hemophilia A.

**Methods****Data search strategy**

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.<sup>10</sup> A computerized and systematic data searching of relevant studies was conducted in PubMed, Scopus, Cochrane Library, Wiley Online Library, and CINAHL (via EBSCOhost) from inception to 16 February 2021. Keywords were constructed based on Medical Subject Headings (MeSH) terms and other additional terms listed as follows: ("rurioctocog alfa pegol" OR "bax 855" OR "TAK-660" OR "SHP660" OR "adynovate" OR "adynovi") AND ("hemophilia A" OR "haemophilia A" OR "factor VIII deficiency" OR "factor 8 deficiency" OR "classic hemophilia" OR "classic haemophilia"). Two reviewers searched the literatures independently. Any disagreements were resolved in a consensus involving a third investigator.

**Eligibility criteria**

Studies were included if the following criteria were met: (1) study design of clinical trial; (2) study population consists of previously treated severe hemophilia A patients with or without healthy subjects as control; (3) rurioctocog alfa

pegol as a prophylactic treatment intervention; and (4) the reported outcomes related to the efficacy, safety, and immunogenicity of rurioctocog alfa pegol (annualized bleeding rate [ABR], patients with zero-bleeding during treatment, hemostatic efficacy, adverse events [AEs], number of deaths, development of FVIII ‘inhibitors’, and/or binding antibodies). The exclusion criteria were as follows: (1) irrelevant titles and abstracts; (2) review articles, systematic reviews, meta-analyses, case reports, case series, letter to editors, and conference abstracts; (3) non-English studies; or (4) irretrievable full-text articles.

### Data extraction and quality assessment

The following relevant data were extracted from the included studies: (1) author and year of publication; (2) study location; (3) clinical trial number; (4) study design; (5) total patients included for prophylactic treatment, gender, and age; (6) definition of target joint (TJ); (7) regimen type; (8) patient characteristics (with or without target joints); (9) total patients in per-protocol analysis set (PPAS) or analyzed for ABR based on regimen type and target joints; (10) outcomes related to efficacy (types of ABR, number of patients with zero-bleeding during treatment, and/or hemostatic efficacy); (11) outcomes related to safety (number of patients with AEs, total AEs, AEs considered related to treatment, and/or number of deaths); and/or (12) outcomes related to immunogenicity (development of FVIII ‘inhibitors’ and/or binding antibodies). The quality assessment of the included studies was performed using the Methodological Index for Non-Randomized Studies (MINORS) scale<sup>11</sup> for non-randomized studies and Modified Jadad scale<sup>12</sup> for randomized studies. Studies with a MINORS score of  $\geq 12$  or a Jadad score of  $\geq 4$  were considered high-quality studies, and the rest were considered low-quality studies. The data extraction and quality assessment were conducted by three reviewers collaboratively through a group discussion and a final decision was taken based on the agreement of all reviewers.

### Statistical analysis

Statistical analyses were performed using the latest version of OpenMeta [Analyst] from the Brown University Evidence-Based Practice Center,<sup>13</sup> MetaXL ver. 5.3 (EpiGear International, Sunrise Beach, Australia), and STATA ver. 16.0 (Stata Corporation, College Station, TX, USA). Single-arm meta-analysis of mean and standard deviation values was performed for four different efficacy outcomes: (1) total ABR; (2) spontaneous ABR; (3) injury ABR; and (4) joint ABR. Whilst, a meta-analysis of proportions was performed for two different efficacy outcomes: (1) zero-bleeding prevalence and (2) hemostatic efficacy with the rating of excellent or good. Subgroup analysis based on target joints (TJs) for total ABR was also performed. For the purpose of meta-analyses, 95% confidence intervals were transformed into standard deviation values based on a method suggested by the Cochrane Handbook Chapter 6.<sup>14</sup>

Heterogeneity between studies was assessed with a chi-square test (Cochran’s  $Q$  statistic) and quantified with the Higgins’  $I^2$  statistics.  $P$ -value  $< 0.1$  from the chi-square test indicated statistical heterogeneity, whereas the level of heterogeneity was determined using  $I^2$  values.  $I^2 < 25\%$  was considered a low heterogeneity, 25–75% a moderate heterogeneity, and  $I^2 > 75\%$  a high heterogeneity. If the  $I^2$  value was greater than 50%, a random-effects model was used for the meta-analysis. Otherwise, a fixed-effects model was applied. Publication bias was explored qualitatively using a funnel plot if the number of studies was adequate ( $n \geq 10$ ). We additionally performed the Egger’s test to quantitatively search for the potential publication bias.  $P$ -value  $< 0.05$  indicated statistical significance in all analyses, unless otherwise stated.

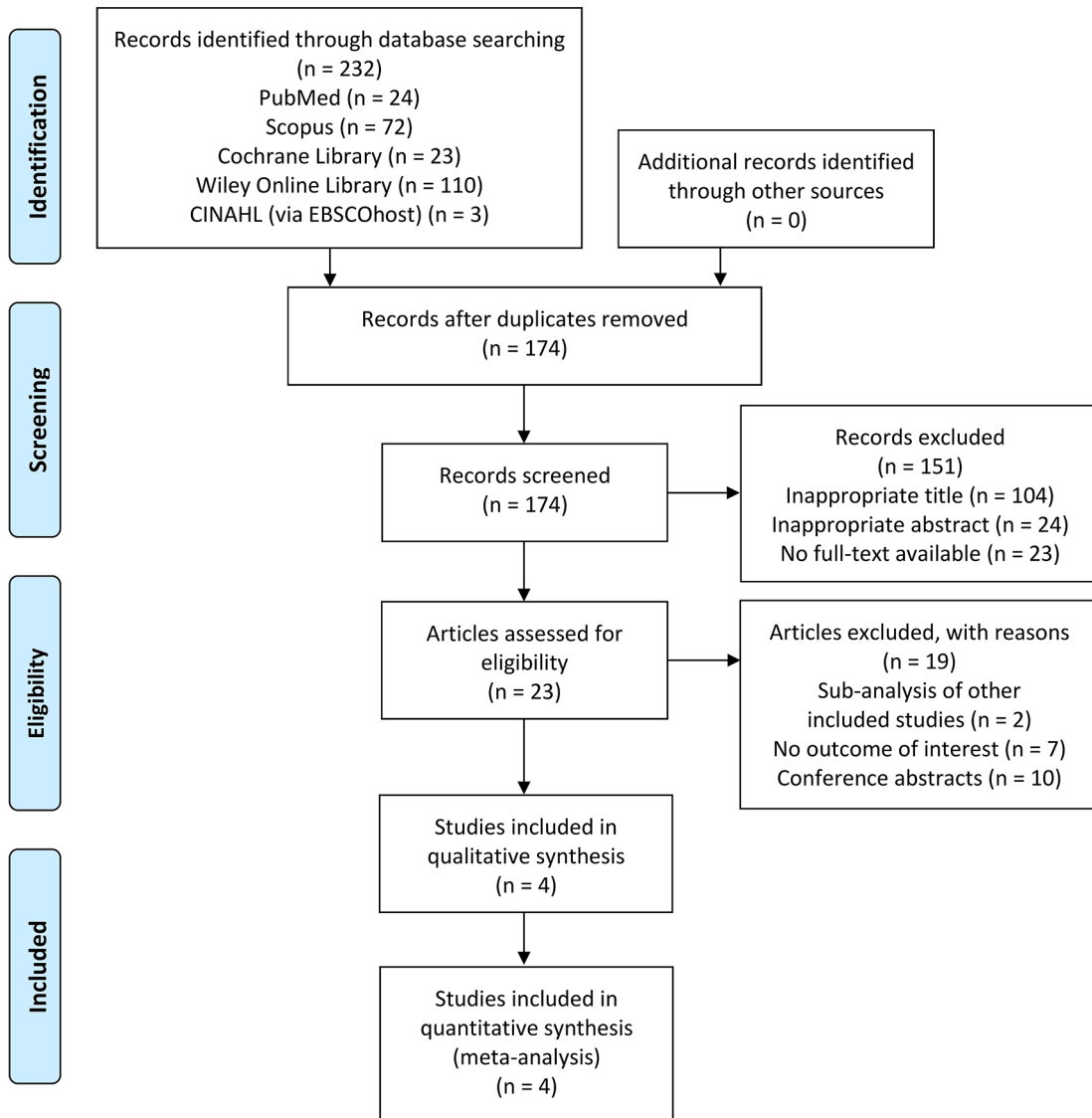
## Results

### Overview of literature search

The initial search of this study yielded a total of 232 articles identified from PubMed, Scopus, Cochrane Library, Wiley Online Library, and CINAHL (via EBSCOhost). Of those, 174 studies were screened by titles and abstracts after duplicates removal. Twenty-three were fully reviewed based on the eligibility criteria and 19 of these were excluded due to: (1) studies with a sub-analysis of other included studies ( $n = 2$ ); (2) not reporting the outcome of interest ( $n = 7$ ); or (3) conference abstracts ( $n = 10$ ). Finally, four clinical trials<sup>5,7,9,15</sup> were included in the qualitative and quantitative synthesis. The overall study selection process is illustrated in [Figure 1](#).

### Characteristics of the included studies

[Table 1](#) provides a summary of the studies included in the systematic review. The four uncontrolled clinical trials<sup>5,7,9,15</sup> included a total of 517 previously treated severe hemophilia A patients for prophylactic treatment, with the overall mean  $\pm$  SD age of  $23.9 \pm 14.8$ . Only two studies by Mullins *et al.*<sup>9</sup> and Chowdary *et al.*<sup>7</sup> included a female patient. The trials were published between 2015 and 2021 and were all multicentered with a range number of 11 to 23 countries. Three<sup>7,9,15</sup> out of four studies were in phase 3 clinical trial, whereas the study by Konkle *et al.*<sup>5</sup> was in a phase 2/3 trial. All studies were non-randomized with the exception of Klamroth *et al.*<sup>15</sup> Definition of target joint was the same across all studies, except for Klamroth *et al.*<sup>15</sup> There were two different prophylactic regimen types used between studies: twice-weekly and pharmacokinetic (PK)-guided. The ‘‘excellent’’ hemostatic efficacy rating was defined as a complete



**Figure 1. PRISMA flow diagram of the study selection process.** PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

resolution of pain and sign of bleedings after a single infusion without the requirement of additional infusion to control the bleeding, while the “good” rating was defined when there was a definite improvement in pain and/or signs of bleeding after a single infusion with a possible requirement of more than one infusion to complete the resolution. The “fair” rating was defined as a slight improvement in pain and/or signs of bleeding after a single infusion with definite requirement of more than one infusion to complete the resolution. If there was no improvement or the condition worsen, the hemostatic efficacy was rated “none”.<sup>5</sup>

### Efficacy outcomes

#### Total ABR

A total of 473 hemophilia A patients from the four studies<sup>5,7,9,15</sup> were included in this subgroup single-arm meta-analysis (Figure 2) to calculate the pooled mean of total ABR after rurioctocog alfa pegol treatment. A random-effects model was used for the analysis since heterogeneity among studies was greater than 50% ( $I^2 = 67%$ ). The overall pooled mean of total ABR was 2.59 (95% CI = 2.04–3.14).

**Table 1.** Characteristics of the included studies.

Author, year	Study location	Clinical trial number	Study design	Total patients included for prophylactic treatment (F)	Age*	Definition of target joint	Total patients in PPAs or analyzed for ABR based on regimen Type & TJ		Spontaneous ABR		Injury ABR		Joint ABR		
							Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	
Mullins <i>et al.</i> , <sup>9</sup> 2017	Multicenter (11 countries)	NCT02210091	Phase 3, open-label, non-randomized, uncontrolled clinical trial	66 (1)	6.0 ± 2.7	A joint (ankles, knees, hips or elbows) with ≥ 3 spontaneous bleeding episodes in any consecutive 6-month period	14	3.54 (1.89–6.64)	4.11	1.20 (0.92–1.56)	2.22	2.09 (1.49–2.93)	2.93	1.10 (0.64–1.91)	2.58
Chowdary <i>et al.</i> , <sup>7</sup> 2020	Multicenter (23 countries)	NCT01945593 (CONTINUATION study)	Phase 3b, open-label, non-randomized, uncontrolled clinical trial	216 (1)	22.8 ± 15.7	A joint with ≥ 3 spontaneous bleeding episodes in any consecutive 6-month period	25	2.64 (1.70–4.08)	1.87	0.96 (0.54–1.71)	0.92	N/A	N/A	1.40 (0.91–2.17)	0.99
Konkle <i>et al.</i> , <sup>5</sup> 2015	Multicenter (20 countries)	NCT01736475 (PROLONG-ATE study)	Phase 2/3, open-label, non-randomized, uncontrolled clinical trial	120 (0)	28.7 ± 9.0	A joint with ≥ 3 spontaneous bleeding episodes in any consecutive 6-month period	69	3.7	4.4	1.9	2.9	N/A	N/A	1.2	2.4
Klamroth <i>et al.</i> , <sup>5</sup> 2020	Multicenter (22 countries)	NCT02585960 (PROPEL study)	Phase 3, open-label, randomized, uncontrolled clinical trial	57 (0)	31.0 ± 13.6	A joint with ≥ 4 spontaneous bleeding episodes in any consecutive 6-month period	32	3	4.9	2.2	3.7	N/A	N/A	2.2	3.2

**Table 1.** Continued

Author, year	Regimen type	Patient characteristics	Total patients in PPAS or analyzed for ABR based on regimen Type & Tj	Total ABR		Spontaneous ABR		Injury ABR		Joint ABR	
				Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD
Klamroth et al., 2020 <sup>15</sup>	PK-guided prophylaxis (1–3%)	With and without Tjs	52	2.8	3	1.7	2.5	1.1	1.9	1.8	2.2
	PK-guided prophylaxis (8–12%)	With and without Tjs	43	1.2	2.4	0.6	1.5	0.7	1.7	0.8	2.3
Author, year	Patients with zero-bleeding during treatment	Hemostatic efficacy		Adverse events					Number of deaths		
		Rating	Events	Total number of bleedings	Number of patients with any AEs (non-SAEs and SAEs)	Total non-SAEs	Non-SAEs considered related to treatment	Number of patients with SAEs	Total SAEs	SAEs considered related to treatment	Number of deaths
Mullins et al., 2017 <sup>9</sup>	25	Excellent Good Fair None Not reported	34 29 4 0 3	70	43	152	0	3	4	0	0
Chowdary et al., 2020 <sup>7</sup>	51	Excellent Good Fair None Not reported	438 368 48 4 52	910	174	786	20	33	52	0	1 (considered unrelated to treatment)
Konkle et al., 2015 <sup>5</sup>	40	Excellent/ Good Fair/ None/ Not reported	498 20	518	73	166	7	5	5	0	0

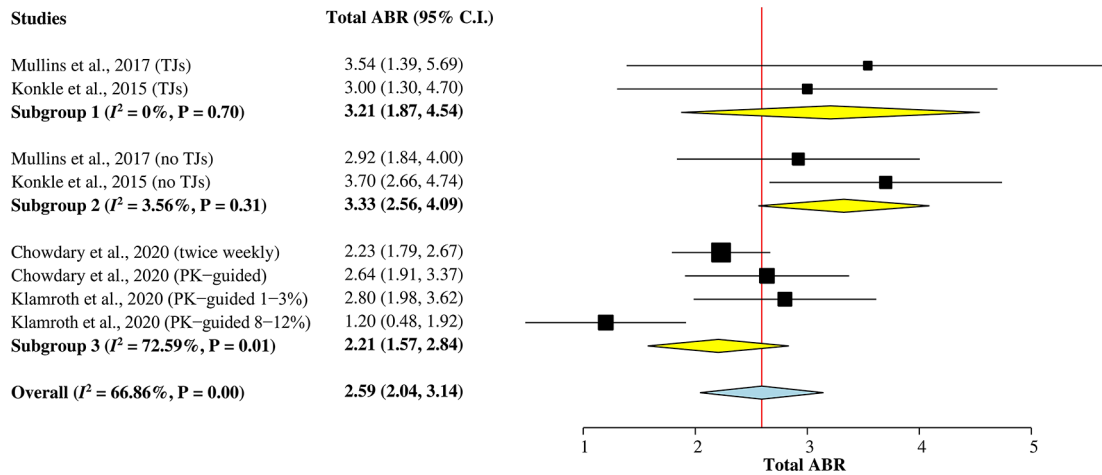


**Table 1.** Continued

Author, year	Patients with zero-bleeding during treatment	Hemostatic efficacy		Adverse events					Number of deaths		
		Rating	Events	Total number of bleedings	Number of patients with any AEs (non-SAEs and SAEs)	Total non-SAEs	Non-SAEs considered related to treatment	Number of patients with SAEs	Total SAEs	SAEs considered related to treatment	
Klamroth <i>et al.</i> , <sup>1,5</sup> 2020	24	N/A	N/A	N/A	34	97	2	3	4	0	0
	36				36	98	1	4	5	1	0
<b>Author, year</b>		<b>Development of FVIII inhibitory antibodies</b>		<b>Development of binding antibodies to FVIII / PEG-FVIII/PEG during study</b>							
Mullins <i>et al.</i> , 2017 <sup>9</sup>		No subjects developed inhibitory antibodies		<ul style="list-style-type: none"> <li>16 developed binding antibodies to FVIII, PEG-FVIII, or PEG prior to exposure, but turned negative while on treatment</li> <li>5 developed antibodies to PEG-VIII during treatment (2 were transient; 2 were only at study completion; and 1 was with decreasing titre)</li> <li>No development of persistent binding antibodies that affected efficacy or safety</li> </ul>							
Chowdhary <i>et al.</i> , 2020 <sup>7</sup>		No subjects developed inhibitory antibodies		<ul style="list-style-type: none"> <li>5 developed binding antibodies to FVIII</li> <li>8 developed binding antibodies to PEG-FVIII</li> <li>Only one persisted to the study end without any notable safety or efficacy findings</li> </ul>							
Konkle <i>et al.</i> , 2015 <sup>5</sup>		No subjects developed inhibitory antibodies		<ul style="list-style-type: none"> <li>7 developed transient binding antibodies to PEG-FVIII or FVIII</li> <li>No subjects developed persistent binding antibodies to FVIII, PEG-FVIII, or PEG</li> <li>Binding antibodies that were detected could not be correlated to impaired treatment efficacy or related AEs</li> </ul>							
Klamroth <i>et al.</i> , 2020 <sup>15</sup>		No subjects developed inhibitory antibodies		<ul style="list-style-type: none"> <li>3 had single positive binding antibodies to PEG-FVIII and PEG at baseline only</li> <li>Binding antibodies that were detected could not be correlated to impaired treatment efficacy or related AEs</li> </ul>							
		1 subject (resolved at the study end)		<ul style="list-style-type: none"> <li>8 developed transient binding antibodies to PEG-FVIII or FVIII.</li> <li>Binding antibodies that were detected could not be correlated to impaired treatment efficacy or related AEs</li> </ul>							

<sup>4</sup>Data are presented in mean ± SD. ABR, annualized bleeding rate; CI, confidence interval; F, female; FVIII, factor VIII; N/A, not available or not applicable; Non-SAEs, non-serious adverse events; PEG, pegylated; PK, pharmacokinetic; PPAS, per-protocol analysis set; SAEs, serious adverse events; SD, standard deviation; Tj(s), target joint(s).





**Figure 2. Forest plot of subgroup single-arm meta-analysis for mean of total ABR.** ABR, annualized bleeding rate; CI, confidence interval; PK, pharmacokinetic; TJ, target joint.

Two studies<sup>5,9</sup> reporting mean of total ABR individually for patients with target joints (TJs) and without target joints were included in Subgroup 1 and Subgroup 2, respectively. The pooled mean of total ABR in patients with TJs was 3.21 (95% CI = 1.87–4.54), whilst the pooled mean of total ABR in patients without TJs was 3.33 (95% CI = 2.56–4.09). Subgroup 3 included other two studies<sup>7,15</sup> with a combined mean of total ABR for patients with and without TJs. The pooled value was 2.21 (95% CI = 1.57–2.84).

*Spontaneous ABR*

The four studies<sup>5,7,9,15</sup> with a total of 473 hemophilia A patients were included in this meta-analysis (Figure 3A). Heterogeneity between studies was greater than 50% ( $I^2 = 64\%$ ); therefore, a random-effects model was used for the analysis. The result of the pooled mean of spontaneous ABR was 1.24 (95% CI = 0.91–1.58).

*Injury ABR*

A total of 161 hemophilia A patients from two studies<sup>9,15</sup> that reported mean of injury ABR were included in this meta-analysis (Figure 3B). A random-effects model was used for the analysis since heterogeneity was greater than 50% ( $I^2 = 80\%$ ). The pooled mean of injury ABR was 1.26 (95% CI = 0.53–1.99).

*Joint ABR*

A total of 473 hemophilia A patients from the four studies<sup>5,7,9,15</sup> were evaluated in this subgroup analysis of joint ABR (Figure 3C). The heterogeneity across studies was low ( $I^2 = 0\%$ ); therefore, a fixed-effects model was used for the analysis. The pooled mean of joint ABR was 1.31 (95% CI = 1.12–1.50).

*Zero-bleeding prevalence*

All four studies<sup>5,7,9,15</sup> were included in this meta-analysis of zero-bleeding prevalence (Figure 4A). A random-effects model was used due to the heterogeneity of the data ( $I^2 = 88\%$ ). The pooled prevalence result was 40% (95% CI = 27%–54%).

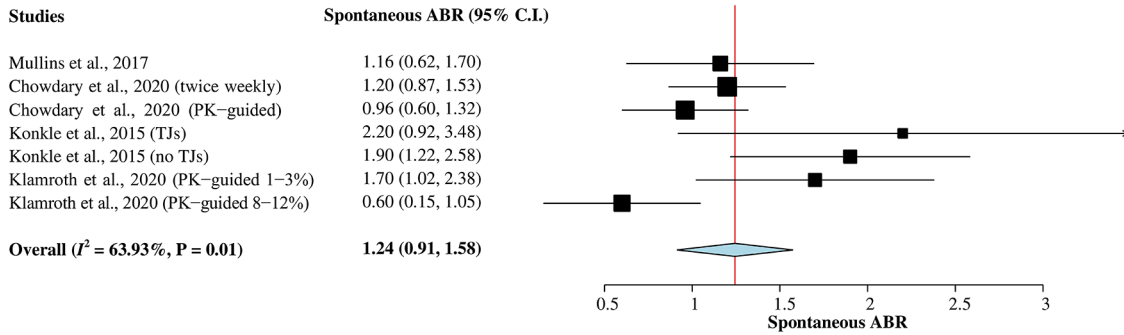
*Hemostatic efficacy*

Three studies<sup>5,7,9</sup> that reported hemostatic efficacy with the rating of excellent or good were included in this meta-analysis (Figure 4B). A random-effects model was used due to the heterogeneity across studies ( $I^2 = 93\%$ ). The pooled hemostatic efficacy was 92% (95% CI = 85%–97%).

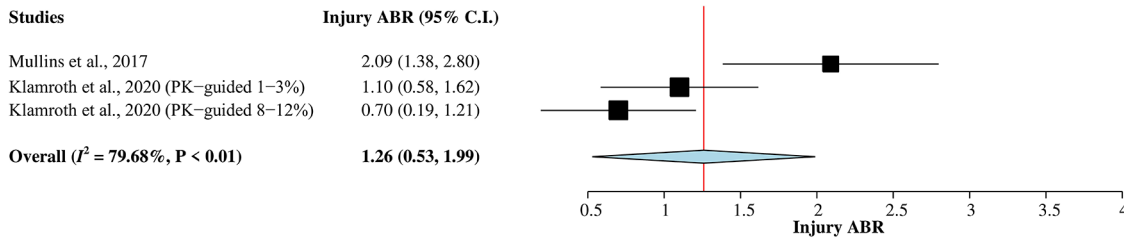
**Safety outcomes**

A total of 1,299 non-serious adverse events (non-SAEs) occurred during the four studies.<sup>5,7,9,15</sup> However, only 30 (2.3%) of them were considered related to rurioctocog alfa pegol treatment. Whilst, a total of 70 serious adverse events (SAEs)

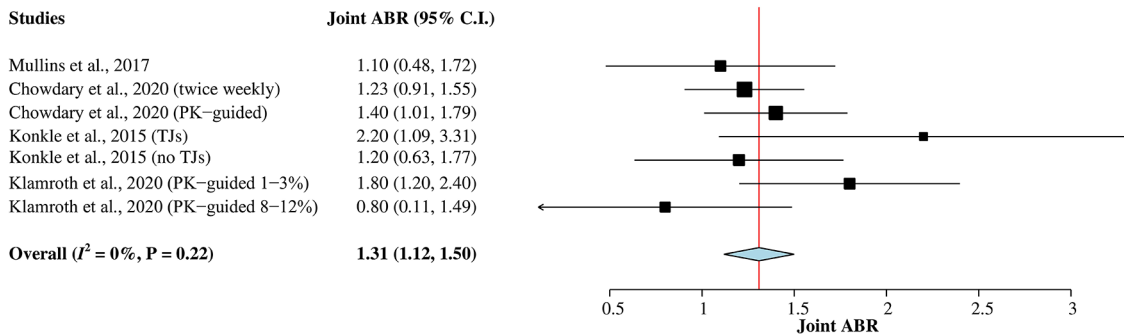
**A**



**B**



**C**



**Figure 3. Forest plots of single-arm meta-analysis for (A) mean of spontaneous ABR, (B) mean of injury ABR, and (C) mean of joint ABR.** ABR, annualized bleeding rate; CI, confidence interval; PK, pharmacokinetic; TJ, target joint.

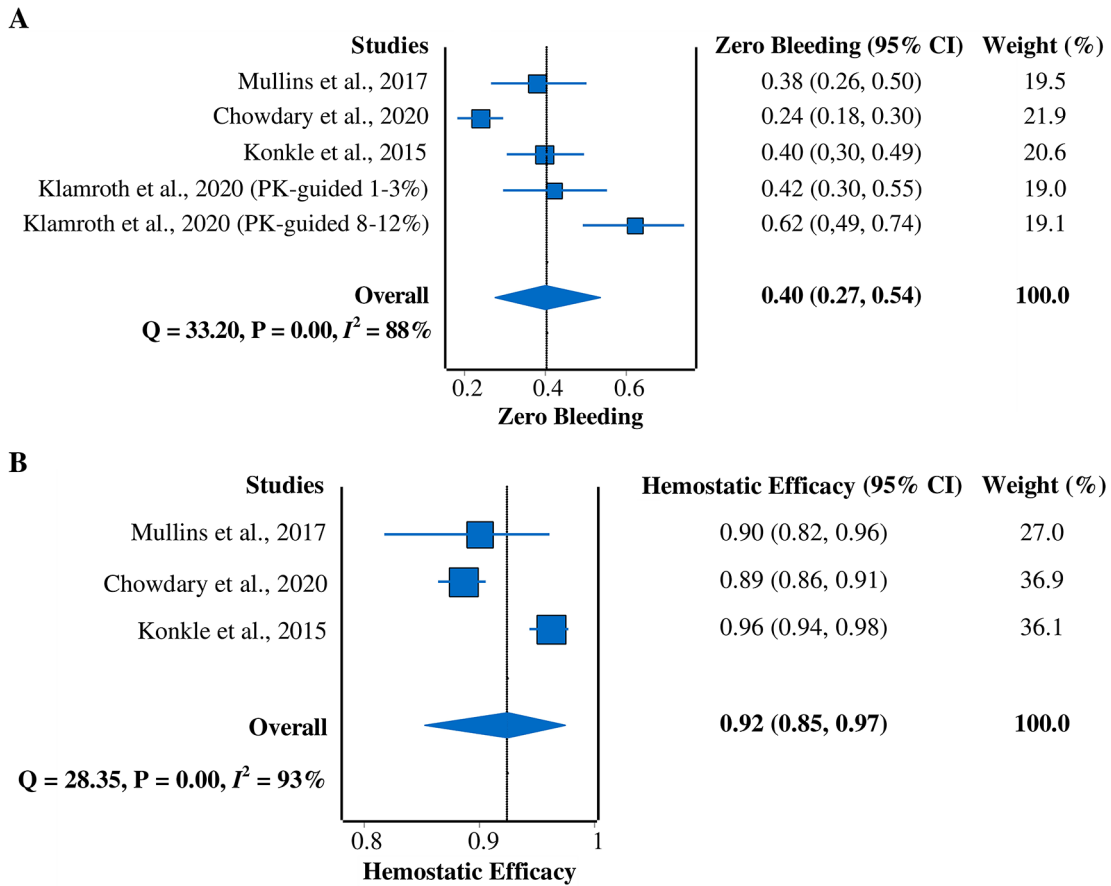
were observed in the four studies and only one (1.4%; a transient development of FVIII inhibitory antibodies) of them – as reported by Klamroth *et al.*<sup>15</sup> – were considered related to treatment. Among all studies, only one death case was reported by Chowdary *et al.*<sup>7</sup> and was not considered to be related to rurioctocog alfa pegol treatment.

**Immunogenicity outcomes**

Three studies<sup>5,7,9</sup> reported no development of FVIII inhibitory antibodies among all patients. Klamroth *et al.*<sup>15</sup> reported one patient with development of FVIII inhibitory antibodies and was resolved at the end of the study. Development of binding antibodies to either FVIII, PEG-FVIII, or PEG among patients was detected in 52 patients from the four studies. However, none of them was correlated to impaired rurioctocog alfa pegol treatment efficacy and AEs.

**Publication bias and quality assessment**

Publication bias assessment using funnel plot was not performed due to the low number of the included studies. The results of the Egger’s tests showed no potential publication bias for total ABR ( $Z = 1.55$ ;  $p = 0.12$ ), joint ABR ( $Z = 0.77$ ;  $p = 0.44$ ), and hemostatic efficacy ( $Z = -0.4$ ;  $p = 0.69$ ). However, we found significant Egger’s test results for spontaneous ABR ( $Z = 2.32$ ;  $p = 0.02$ ), injury ABR ( $Z = 2.99$ ;  $p = 0.003$ ), and zero-bleeding prevalence ( $Z = 2.59$ ;  $p = 0.01$ ). Details of the quality assessment using MINORS and Modified Jadad scale are provided in Table 2. All non-randomized studies<sup>5,7,9</sup> were considered high in quality, whereas the randomized study by Klamroth *et al.*<sup>15</sup> was considered low in quality.



**Figure 4.** Forest plots of meta-analysis of proportions for (A) zero-bleeding prevalence and (B) hemostatic efficacy (excellent or good rating). CI, confidence interval; PK, pharmacokinetic.

**Table 2.** Summary of quality assessment using MINORS and Modified Jadad Scale.

MINORS Scale			Modified Jadad Scale	
Items	Mullins et al., 2017 <sup>9</sup>	Chowdary et al., 2020 <sup>7</sup>	Items	Klamroth et al., 2020 <sup>15</sup>
A clearly stated aim	2	2	Randomization	1
Inclusion of consecutive patients	2	2		
Prospective collection of data	2	2	Concealment	0
Endpoints appropriate to the aim of the study	2	2		
Unbiased assessment of the study endpoint	0	0	Blinding	0
Follow-up period appropriate to the aim of the study	2	2		
Loss to follow up less than 5%	2	2	Withdrawal or drop-out	1
Prospective calculation of the study size	1	1		
<b>Results</b>			<b>Results</b>	
<b>Total score</b>	13	13	<b>Total score</b>	2
<b>Study quality</b>	High	High	<b>Study quality</b>	Low

MINORS, Methodological Index for Non-Randomized Studies.

## Discussion

This study was the first far-reaching, single-arm meta-analysis that evaluates the efficacy, safety, and immunogenicity of rurioctocog alfa pegol, a newly developed rFVIII product with a prolonged half-life, as a prophylactic treatment for previously treated patients with severe hemophilia A. Rurioctocog alfa pegol (BAX 855) is a pegylated full-length rFVIII product designed to reduce the frequency of prophylactic infusions while maintaining hemostatic efficacy in patients with hemophilia.<sup>16,17</sup> This study indicated the long-term safety and efficacy of the pharmacological agent, which were consistent with the study of rurioctocog alfa pegol for perioperative hemostasis in hemophilia A patients,<sup>18,19</sup> also with the previous parent studies.<sup>20–22</sup>

The overall pooled mean of total ABR of rurioctocog alfa pegol is lower compared to the several conventional rFVIII (Advate<sup>®</sup>, Xyntha<sup>®</sup>, Novoeight<sup>®</sup>, REFACTO<sup>®</sup>) with their total ABR ranged from 3.3 to 6.5.<sup>23</sup> The ABR of rurioctocog alfa was also lower compared to simoctocog alfa (Nuwiq<sup>®</sup>), a B-domain deleted rFVIII (2.59 vs. 2.91), administered every two days.<sup>24</sup> This could indicate that rurioctocog alfa pegol offers both the higher and long-term efficacy over conventional and other type of rFVIII. Compared to other extended half-life rFVIII from another study, we found a lower ABR for rurioctocog alfa pegol than efmoroctocog alfa (Eloctate<sup>®</sup>; 2.59 vs. 4.90).<sup>25</sup> Interestingly, a study by Reding *et al.*<sup>26</sup> showed a lower ABR (1.49) for another novel extended half-life rFVIII, damoctocog alfa pegol (Jivi<sup>®</sup>), than our study finding. This product is potential to be used as other alternative long-term treatments for hemophilia A, but it is still necessary to confirm its efficacy with more clinical trials.

The spontaneous- and injury-related bleeding are important evaluations for hemophilia, especially in prophylactic treatment use.<sup>27</sup> Without an appropriate prophylactic treatment, patients have a tendency to experience monthly spontaneous bleeding episodes (including spontaneous joint bleeds) and prolonged and excessive bleeding after minor trauma.<sup>28,29</sup> Our results showed that the ABRs of rurioctocog alfa pegol were similar for spontaneous- and injury-related bleeding. This indicates that rucioctocog alfa pegol can be used to prevent both of conditions. It is also important to evaluate the efficacy of hemophilia treatment for patients with target joints. Untreated bleeding creates a persistent inflammatory response that leads to irreversible changes in the joints, resulting in hemophilic arthropathy and permanent disability.<sup>30</sup> Any reduction in joint bleeds is considered an improvement in quality of life for hemophilia patients.<sup>31</sup> Decreased bleeding in joints thereby shows better joint health, activity, and satisfaction for the patients.<sup>32</sup> The pooled mean ABR for patients with target joints was similar to those without target joints, indicating that rurioctocog alfa pegol had an equal efficacy for both groups of patients. Moreover, all studies reported that rurioctocog alfa pegol had higher good and excellent hemostatic efficacy events. This data was comparable with results reported for other rFVIII preparations.<sup>33–36</sup> The efficacy of rurioctocog alfa pegol was also supported by the finding on the pooled zero-bleeding prevalence.

Our study also demonstrated the safety of rurioctocog alfa pegol in patients by assessing the non-SAEs and SAEs. Rurioctocog alfa pegol was proven acceptable and safe for perioperative hemostasis, with minor findings in both non-SAEs and SAEs.<sup>18</sup> Our data showed that most of the adverse reactions were mild, and the prevalence seems rarer than damoctocog alfa pegol (79%–95% patients with AEs).<sup>26,37</sup> Additionally, all rFVIII usage decreased the risk of blood-borne infections and restored longer life expectancies.<sup>38</sup> As extended half-life rFVIII, they can also improve adherence to prophylactic regimens and reduce the burden of treatment.<sup>39,40</sup> However, there are some concerns regarding the safety of PEG component, particularly when it is used for lifelong prophylaxis. Nevertheless, the PEG levels found in rurioctocog alfa pegol were minimal (less than 1 mg/dose) and evidence has showed no specific side effects to central nervous system, liver, or kidney.<sup>41</sup>

The development of FVIII ‘inhibitors’ is a major issue in patients treated with blood coagulation factor products. The development of neutralizing alloantibodies against FVIII can reduce the treatment benefits.<sup>42,43</sup> Currently available studies revealed some predictors of ‘inhibitor’ development, but the predictive power remained low.<sup>44,45</sup> Several studies reported either transient or persistent ‘inhibitor’ development in patients treated with plasma-derived FVIII.<sup>46,47</sup> Interestingly, the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study revealed lower incidence of ‘inhibitor’ development in previously untreated patients whom treated with plasma-derived FVIII products compared to rFVIII products.<sup>48</sup> This finding attracted a lot of debate among experts, but we yet have to take notice of it to further improve the quality of future rFVIII products. However, our findings showed no development of persistent FVIII inhibitory antibodies, and this was consistent with the US Food and Drug Administration's approval of rurioctocog alfa pegol for the treatment of hemophilia A patients.<sup>49</sup> There was some development of binding antibodies observed. However, this development did not interfere with rurioctocog alfa pegol treatment safety and efficacy until the end of the study. Although this finding may look favorable, all the patients included in our study were previously treated patients. The development of ‘inhibitors’ tends to be rarer in these patients than previously untreated patients.<sup>50</sup> Furthermore, all the included studies excluded patients with the history of and detectable FVIII ‘inhibitors’ at screening before

recruitment.<sup>5,7,9,15</sup> Hence, we could assume that positive individual factors of ‘inhibitor’ development, such as underlying gene defects and family history,<sup>43,51</sup> might not be present in these patients, since they had been screened previously. Nevertheless, there is still no strong evidence of association between switching types of treatment with the development of ‘inhibitors’ in previously treated patients. Therefore, shifting to other types of treatment might be considered if it is more beneficial for the patients.<sup>52</sup>

Overall, our study successfully demonstrated the pooled efficacy, safety, and immunogenicity of rurioctocog alfa pegol as a treatment for hemophilia A. These results can be used to plan an alternative treatment for hemophilia A patients. Nevertheless, high heterogeneity existed between the included studies. We used the random-effects model to minimize this issue. Substantial efforts were made to explore the possible source for heterogeneity, revealing that different dose regimens and prior prophylactic drugs for treatment could be responsible for the high heterogeneity. Regarding the zero-bleeding prevalence (Figure 4A), a difference in the administered dose regimens was observed among studies. Different dose regimens were considered because pharmacokinetic profiles, targets of FVIII level, and age group varied among patients. The PK-guided dosing was applied to provide more individualized prophylaxis according to each patient’s PK profiles (e.g., plasma half-life), targets of FVIII level, and body weight. Age is also a determining factor since it influences the PK profiles.<sup>6</sup>

Several other limitations exist in this meta-analysis. First, our study only included single-arm clinical trials. The highest possible quality cannot be ensured due to the lack of control arms. However, since hemophilia is a rare genetic disease, comparison with a control arm receiving prophylaxis with other conventional FVIII products was not recommended, as stated by the regulatory guide.<sup>53</sup> Second, diverse prior prophylactic strategies in the patients before switching to rurioctocog alfa pegol may affect the treatment outcomes. Third, publication was observed for several outcomes, and thus the results should be interpreted carefully. Finally, only a few published studies were evaluated in this meta-analysis since rurioctocog alfa pegol is a newly-developed drug. However, these limitations were partly compensated by the multicentered settings of the included studies.

## Conclusions

Our study suggests that rurioctocog alfa pegol is effective, safe, and has low immunogenicity for previously treated patients with severe hemophilia A. Despite the lack of direct comparison studies, rurioctocog alfa pegol could serve as an alternative bleeding prophylaxis in hemophilia A. A network meta-analysis with a multi-arm approach on hemophilia A treatment is warranted to corroborate the current evidence.

## Data availability

All data underlying the results are available as part of the article and no additional source data are required.

## Reporting guidelines

Open Science Framework: PRISMA Checklist for “Efficacy, Safety, and Immunogenicity of Rurioctocog Alfa Pegol for Prophylactic Treatment in Previously Treated Patients with Severe Hemophilia A: A Systematic Review and Meta-Analysis of Clinical Trials”. <https://doi.org/10.17605/OSF.IO/4EZAG>.<sup>54</sup>

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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# Open Peer Review

Current Peer Review Status:  

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## Version 3

Reviewer Report 24 January 2022

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**Claudia Djambas Khayat** 

Hospital Hôtel Dieu de France, Saint Joseph University, Beirut, Lebanon

The modifications done in the manuscript satisfy me. I have no further comments to make.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Hemophilia and rare Bleeding disorders

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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## Version 2

Reviewer Report 03 December 2021

<https://doi.org/10.5256/f1000research.79147.r99803>

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**Claudia Djambas Khayat** 

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The authors aim to evaluate the efficacy, safety, and immunogenicity of ruriotocog alfa pegol, in previously treated patients with severe hemophilia A through a systematic review and meta-analysis. Unfortunately, the study only included only 4 single-arm, industry sponsored, clinical trials. This is a significant limitation for the study conclusion. Real life data and non-sponsor

studies are needed to set up a strong meta-analysis

Several remarks concerning the study:

- The introduction is not adequate for the subject. The introduction to hemophilia should be more concise. It will be better to discuss more through the introduction of the importance and burden of regular prophylaxis and the theoretical importance of extended half life in general.
- Concerning the eligible studies. In the discussion you state that this study indicated the long-term safety and efficacy of the pharmacological agent, which were consistent with the study of rurioctocog alfa pegol for perioperative hemostasis in hemophilia A patients [18,19]. - Why were these 2 studies not included in the meta-analysis for safety and efficacy?
- "The overall pooled mean of total ABR of rurioctocog alfa pegol is lower compared to the several conventional rFVIIIs". - You should have also compared rurioctocog alpha pegol to the other extended half-life product.
- "This extended half-life recombinant also improved adherence to prophylactic regimen and reduced the burden of treatment". - This statement is not shown in your result.
- You add a new reference in the discussion - a very good one but it will be better to correct the numbering of the reference.
- "The development of FVIII 'inhibitors' is a major issue in patients", "our findings showed no development of persistent FVIII inhibitory antibodies" - You should discuss the fact that all patients are previously treated patients. You are not selling a product, you should do meta-analysis for scientific purposes.
- In fact, the discussion is a little bit superficial. There is no real discussion, just putting the result in a different way.

This article does not have additional value to what is already written like it is.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Yes

**Is the statistical analysis and its interpretation appropriate?**

Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Hemophilia and rare Bleeding disorders

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 28 Dec 2021

**Citrawati Wungu**, Universitas Airlangga, Surabaya, Indonesia

We would like to thank the reviewer for reading and commenting on our submission. We will attempt to answer each question and suggestion as clearly as possible. Hopefully, revisions made on the manuscript would allow further considerations on indexing the article.

### **Reviewer 2**

Thank you for reviewing our manuscript. We hereby list the responses and revisions made on the original manuscript:

1. The introduction is not adequate for the subject. The introduction to hemophilia should be more concise. It will be better to discuss more through the introduction of the importance and burden of regular prophylaxis and the theoretical importance of extended half life in general.

**Answer:** Thank you for the suggestion. We have removed unnecessary information to shorten the introduction to hemophilia and added additional information regarding the importance, burden, and theoretical importance of extended half-life rFVIII in the introduction section.

2. Concerning the eligible studies. In the discussion you state that this study indicated the long-term safety and efficacy of the pharmacological agent, which were consistent with the study of rurioctocog alfa pegol for perioperative hemostasis in hemophilia A patients [18,19]. - Why were these 2 studies not included in the meta-analysis for safety and efficacy?

**Answer:** We did not include the 2 studies since the study aimed to specifically review the role of rurioctocog alfa pegol as a prophylactic treatment. We acknowledged that treatment is different from perioperative hemostasis, in which treatment for hemophilia A considers more regarding the management of patients to prevent their daily bleedings. In order to focus the paper to the prophylactic properties of rurioctocog alfa pegol, we excluded them in this systematic review.

3. "The overall pooled mean of total ABR of rurioctocog alfa pegol is lower compared to the several conventional rFVIIIs". - You should have also compared rurioctocog alpha pegol to the other extended half-life product.

**Answer:** Thank you for the insightful feedback. We have added additional comparison of rurioctocog alfa pegol with other extended half-life products in the discussion section.

4. "This extended half-life recombinant also improved adherence to prophylactic regimen

and reduced the burden of treatment". - This statement is not shown in your result.

**Answer:** Thank you for the constructive comment. We would like to apologize for the unclarity of the sentence. This sentence was not related to the study result and was intended to add information regarding the advantage of extended half-life rFVIIIs products, such as rurioctocog alfa pegol. In regard to this, we would like to revise and correct the structure of the mentioned sentences to avoid misunderstanding.

5. You add a new reference in the discussion - a very good one but it will be better to correct the numbering of the reference.

**Answer:** Thank you for the meticulous observation. We would like to apologize as there were errors during the numbering input. We have revised the numbering of the references to the correct order.

6. "The development of FVIII 'inhibitors' is a major issue in patients", "our findings showed no development of persistent FVIII inhibitory antibodies" - You should discuss the fact that all patients are previously treated patients. You are not selling a product, you should do meta-analysis for scientific purposes.

**Answer:** Thank you for the valuable suggestion. We acknowledged that we have not sufficiently discussed regarding the immunogenicity properties of rurioctocog alfa pegol since the patients are all previously treated. We have added additional information in the discussion section. We hope that the revised discussion could provide more objective perspective in choosing treatment for hemophilia A patients.

7. In fact, the discussion is a little bit superficial. There is no real discussion, just putting the result in a different way. This article does not have additional value to what is already written like it is.

**Answer:** We really appreciate this very useful feedback as well and we have added more contents for the discussion. We hope that the added information are sufficient to provide more in-depth discussion.

#### **Additional Information**

We thank the reviewer for giving us an opportunity to improve our manuscript. We have added an additional analysis, the Egger's test, to explore the potential of publication bias in all outcomes. Accordingly, we included additional details in the method, result, and discussion sections regarding the Egger's test. We hope that this insertion could further provide additional value to the study findings.

**Competing Interests:** We declare that we have no competing interest

Reviewer Report 12 November 2021

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**Yelvi Levani** 

Faculty of Medicine, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia

The author has been revised the article according to reviewer's comment. Therefore, no further comments needed.

Thank you.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Yes

**Is the statistical analysis and its interpretation appropriate?**

Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Immunology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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Version 1

Reviewer Report 02 November 2021

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**Yelvi Levani** 

Faculty of Medicine, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia

This paper is clearly written and well organized. This paper presented the meta analysis of the

efficacy, safety and immunogenicity of newly developed drug for severe hemophilia A, rurioctocog alfa pegol. The figures and tables are also clear and helpful.

However, there are some parts that need clarifying:

- In the result part (section: safety outcomes) the author stated: "A total of 1,299 non-serious adverse events (non-SAEs) occurred during the four studies.<sup>5,7,9,15</sup> However, only 30 (2.3%) of them were considered related to rurioctocog alfa pegol treatment. Whilst, a total of 70 serious adverse events (SAEs) were observed in the four studies and only one (1.4%) of them – as reported by Klamroth et al.<sup>15</sup> – were considered related to treatment" - I think it would be nicer, if author gives more explanation or examples about what kind of serious adverse that related to rurioctocog alfa pegol treatment.
- In the discussion part, the author stated, "Regarding the zero-bleeding prevalence (Figure 4A), a difference was observed among studies that employed different dose regimens. Different dose regimens were considered because pharmacokinetic profiles, targets of FVIII level, and age group varied among patients." - I think it would be better if the authors explain more about the dose regimens and pharmacokinetic in the introduction or discussion part.

I added a reference from Stidl et al. (2018)<sup>1</sup>, because the article explained about the safety and potential adverse effects that related to rurioctocog alfa pegol. This reference could help enrich the discussion of article, especially in the part of safety and adverse effects from the drug.

Overall, this article is interesting and gives valuable information.

## References

1. Stidl R, Denne M, Goldstine J, Kadish B, et al.: Polyethylene Glycol Exposure with Antihemophilic Factor (Recombinant), PEGylated (rurioctocog alfa pegol) and Other Therapies Indicated for the Pediatric Population: History and Safety. *Pharmaceuticals (Basel)*. 2018; **11** (3). [PubMed Abstract](#) | [Publisher Full Text](#)

## Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

## Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

## Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

## Are the conclusions drawn adequately supported by the results presented in the review?

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Immunology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 04 Nov 2021

**Citrawati Wungu**, Universitas Airlangga, Surabaya, Indonesia

We would like to thank the reviewer for reading and commenting on our submission. We will attempt to answer each question and suggestion as clearly as possible. Hopefully, revisions made on the manuscript would allow further considerations on indexing the article.

We hereby list the responses and revisions made on the original manuscript:

1. In the result part (section: safety outcomes) the author stated: "A total of 1,299 non-serious adverse events (non-SAEs) occurred during the four studies.<sup>5,7,9,15</sup> However, only 30 (2.3%) of them were considered related to rurioctocog alfa pegol treatment. Whilst, a total of 70 serious adverse events (SAEs) were observed in the four studies and only one (1.4%) of them – as reported by Klamroth *et al.*<sup>15</sup> – were considered related to treatment" - I think it would be nicer, if author gives more explanation or examples about what kind of serious adverse that related to rurioctocog alfa pegol treatment.

**Answer:** Thank you for the suggestion. We have added an additional information regarding the serious adverse event occurred related to the treatment as reported by Klamroth *et al.*<sup>15</sup> in the safety outcomes section of the result part.

2. In the discussion part, the author stated, "Regarding the zero-bleeding prevalence (Figure 4A), a difference was observed among studies that employed different dose regimens. Different dose regimens were considered because pharmacokinetic profiles, targets of FVIII level, and age group varied among patients." - I think it would be better if the authors explain more about the dose regimens and pharmacokinetic in the introduction or discussion part.

**Answer:** We have provided further explanation regarding the dose regimens and pharmacokinetic in the discussion part. We would also like to revise and correct the structure of the mentioned sentences to avoid unclarity.

3. I added a reference from Stidl *et al.* (2018)<sup>1</sup>, because the article explained about the safety and potential adverse effects that related to rurioctocog alfa pegol. This reference could help enrich the discussion of article, especially in the part of safety and adverse effects from the drug.

Stidl R, Denne M, Goldstine J, Kadish B, et al.: Polyethylene Glycol Exposure with Antihemophilic Factor (Recombinant), PEGylated (rurioctocog alfa pegol) and Other Therapies Indicated for the Pediatric Population: History and Safety. *Pharmaceuticals* (Basel). 2018; 11 (3). PubMed Abstract | Publisher Full Text

**Answer:** Thank you for the recommendation. We have added an additional description related to safety based on the suggested reference.



**Competing Interests:** We declare that we have no competing interest.

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