

SUPPLEMENTARY MATERIAL

Efficacy and safety of recombinant factor VIII in previously untreated and previously treated children with hemophilia A: a systematic review

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Table S1: Search strategy

PubMed			
#1:	((((((((Hemophilia A[Title/Abstract]) OR (Hemophilia A[MeSH Terms])) OR (Hemophilia*[Title/Abstract])) OR (hemophilia*[Title/Abstract])) OR (haemophilia*[Title/Abstract])) OR (hemophil*[Title/Abstract])) OR (haemophil*[Title/Abstract])) NOT (acquired*[Title/Abstract])) NOT (Animals[MeSH Terms])	OR	
#2:	((((((((((((Children[Title/Abstract]) OR (child[Title/Abstract])) OR (Pediatrics[Title/Abstract])) OR (Paediatrician[Title/Abstract])) OR (pediatr[Title/Abstract])) OR (≤12[Title/Abstract])) OR (<12[Title/Abstract])) OR (≤6[Title/Abstract])) OR (<6[Title/Abstract])) OR (childhood[Title/Abstract])) OR (previously treated patient[Title/Abstract])) OR (PTP[Title/Abstract])) OR (previously untreated patient[Title/Abstract])) OR (PUP[Title/Abstract])) OR (PUPs[Title/Abstract])) OR (minimally treated patient[Title/Abstract])) OR (MTP[Title/Abstract])	OR	
#3:	((((((((((((((((((((Factor VIII[Title/Abstract]) OR (Factor VIIIA[Title/Abstract])) OR (coagulation factor VIII[Title/Abstract])) OR (recombinant factor VIII[Title/Abstract])) OR (rFVIII[Title/Abstract])) OR (F8 protein[Title/Abstract])) OR (Octocog alfa[Title/Abstract])) OR (Recombinate®[Title/Abstract])) OR (Helixate FS®[Title/Abstract])) OR (Kogenate FS®[Title/Abstract])) OR (Advate®[Title/Abstract])) OR (Kovaltry®[Title/Abstract])) OR (Moroctocog alfa[Title/Abstract])) OR (Xyntha®[Title/Abstract])) OR (ReFacto AF®[Title/Abstract])) OR (Turoctocog alfa[Title/Abstract])) OR (Novoeight®[Title/Abstract])) OR (Lonoctocog alfa[Title/Abstract])) OR (Afstyla®[Title/Abstract])) OR (Simoctocog alfa[Title/Abstract])) OR (Nuwiq®[Title/Abstract])) OR (Ruriotacog alfa pegol[Title/Abstract])) OR (Adynovate®[Title/Abstract])) OR (Damoctocog alfa pegol[Title/Abstract])) OR (Jivi®[Title/Abstract])) OR (Turoctocog alfa pegol[Title/Abstract])) OR (N8-GP[Title/Abstract])) OR (Esperoct®[Title/Abstract])) OR (Efmoctocog alfa[Title/Abstract])) OR (Eloctate®[Title/Abstract])) OR (ALTUVIIIIO[Title/Abstract])	OR	
#4:	((((((((Clinical Trial[Publication Type]) OR (real world[Title/Abstract])) OR (research[Title/Abstract])) OR (randomized controlled trials[Title/Abstract])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (open label[Title/Abstract])) OR	OR	

(trials[Title/Abstract])) OR (trial[Title/Abstract])

#5: #1 AND #2 AND #3 AND #4

Embase

#1: ('hemophilia a':ab,ti OR 'hemophilia a'/exp OR hemophilia*:ab,ti OR haemophilia*:ab,ti OR hemophil*:ab,ti OR haemophil*:ab,ti) NOT acquired*:ab,ti NOT 'animals'/exp

#2: 'Children':ab,ti OR 'child':ab,ti OR 'Pediatrics':ab,ti OR 'Paediatrician':ab,ti OR 'pediatry':ab,ti OR '≤12':ab,ti OR '<12':ab,ti OR '≤6':ab,ti OR '<6':ab,ti OR 'childhood':ab,ti OR 'previously treated patient':ab,ti OR 'PTP':ab,ti OR 'previously untreated patient':ab,ti OR 'PUP':ab,ti OR 'PUPs':ab,ti OR 'minimally treated patient':ab,ti OR 'MTP':ab,ti

#3: 'Factor VIII':ab,ti OR 'Factor VIIIA':ab,ti OR 'coagulation factor VIII':ab,ti OR 'recombinant factor VIII':ab,ti OR 'rFVIII':ab,ti OR 'F8 protein':ab,ti OR 'Recombinate®':ab,ti OR 'Helixate FS®':ab,ti OR 'Kogenate FS®':ab,ti OR 'Advate®':ab,ti OR 'Kovaltry®':ab,ti OR 'Moroctocog alfa':ab,ti OR 'Xyntha®':ab,ti OR 'ReFacto AF®':ab,ti OR 'Turoctocog alfa':ab,ti OR 'Novoeight®':ab,ti OR 'Lonoctocog alfa':ab,ti OR 'Afstyla®':ab,ti OR 'Simoctocog alfa':ab,ti OR 'Nuwiq®':ab,ti OR 'Ruriotocog alfa pegol':ab,ti OR 'Adynovate®':ab,ti OR 'Damoctocog alfa pegol':ab,ti OR 'Jivi®':ab,ti OR 'Turoctocog alfa pegol':ab,ti OR 'N8-GP':ab,ti OR 'Esperoct®':ab,ti OR 'Efmorotocog alfa':ab,ti OR 'Eloctate®':ab,ti OR 'ALTUVIIIOTM': ab,ti

#4: 'real world':ab,ti OR 'research':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'open label':ab,ti OR 'trials':ab,ti OR 'trial':ab,ti

#5: #1 AND #2 AND #3 AND #4

Cochrane Library

#1: 'hemophilia a':ti,ab,kw OR hemophilia*:ti,ab,kw OR haemophilia*:ti,ab,kw OR hemophil*:ti,ab,kw OR haemophil*:ti,ab,kw NOT acquired*:ti,ab,kw NOT 'animals':ti,ab,kw

#2: 'Children':ti,ab,kw OR 'child':ti,ab,kw OR 'Pediatrics':ti,ab,kw OR 'Paediatrician':ti,ab,kw OR 'pediatry':ti,ab,kw OR '≤12':ti,ab,kw OR '<12':ti,ab,kw OR '≤6':ti,ab,kw OR '<6':ti,ab,kw OR 'childhood':ti,ab,kw OR 'previously treated patient':ti,ab,kw OR 'PTP':ti,ab,kw OR 'previously untreated patient':ti,ab,kw OR 'PUP':ti,ab,kw OR 'PUPs':ti,ab,kw OR 'minimally treated patient':ti,ab,kw OR 'MTP':ti,ab,kw

#3: 'Factor VIII':ti,ab,kw OR 'Factor VIIIA':ti,ab,kw OR 'coagulation factor VIII':ti,ab,kw OR

'recombinant factor VIII':ti,ab,kw OR 'rFVIII':ti,ab,kw OR 'F8 protein':ti,ab,kw OR 'Recombinate®':ti,ab,kw OR 'Helixate FS®':ti,ab,kw OR 'Kogenate FS®':ti,ab,kw OR 'Advate®':ti,ab,kw OR 'Kovaltry®':ti,ab,kw OR 'Moroctocog alfa':ti,ab,kw OR 'Xyntha®':ti,ab,kw OR 'ReFacto AF®':ti,ab,kw OR 'Turoctocog alfa':ti,ab,kw OR 'Novoeight®':ti,ab,kw OR 'Lonoctocog alfa':ti,ab,kw OR 'Afstyla®':ti,ab,kw OR 'Simoctocog alfa':ti,ab,kw OR 'Nuwiq®':ti,ab,kw OR 'Rurioctacog alfa pegol':ti,ab,kw OR 'Adynovate®':ti,ab,kw OR 'Damoctocog alfa pegol':ti,ab,kw OR 'Jivi®':ti,ab,kw OR 'Turoctocog alfa pegol':ti,ab,kw OR 'N8-GP':ti,ab,kw OR 'Esperoct®':ti,ab,kw OR 'Efmoctocog alfa':ti,ab,kw OR 'Eloctate®':ti,ab,kw OR 'ALTUVIIIOTM': ti,ab,kw

#4: 'real world':ti,ab,kw OR 'research':ti,ab,kw OR 'randomized controlled trials':ti,ab,kw OR 'randomized':ti,ab,kw OR 'placebo':ti,ab,kw OR 'open label':ti,ab,kw OR 'trials':ti,ab,kw OR 'trial':ti,ab,kw

Table S2: Sensitivity analysis. Pooled proportion of inhibitor development by the product type (studies with patients > 50).

Variable	N	Events/Total	Pooled estimate (95% CI)	τ^2
Overall study	8	192/707	25.2% (15.7%; 36.0%)	0.025
PTPs	1	1/69	NA	NA
PUPs	7	191/638	29.9% (25.8%; 34.1%)	<0.001
Third generation SHL	3	104/323	33.5% (25.1%; 42.5%)	0.004
rFVIII length				
Full-length rFVIII	1	44/162	NA	NA
B-domain deleted rFVIII	2	60/161	37.5% (29.0%; 46.4%)	0.001
EHL	4	87/315	27.5% (22.6%; 32.6%)	<0.001

Notes: SHL, standard half-life; EHL, extended half-life; PUPs, previously untreated patients; PTPs, previously treated patients; MTPs, minimally treated patients; FVIII, factor VIII; rFVIII, recombinant FVIII; CI, confidence interval; τ^2 , Tau², between-study variance; N, the number of studies included in the analysis; NA, not available. In the sensitivity analysis of inhibitor incidence, MTPs were excluded from the population of PUPs.

Table S3: Sensitivity analysis. Pooled proportion of treatment-related AEs (studies with patients > 50).

Variable	N	Events/Total	Pooled estimate (95% CI)	τ^2
Overall study	11	322/747	36.2% (15.9%; 59.5%)	0.149
PTPs	6	134/408	24.7% (2.7%; 58.0%)	0.177
Third generation SHL	2	55/122	35.5% (0.0%; 99.7%)	0.356
EHL	4	79/286	19.8% (0.0%; 58.3%)	0.164
PUPs	5	188/339	51.2% (23.6%; 78.4%)	0.102
Third generation SHL	2	52/115	42.6% (0.3%; 94.8%)	0.19
rFVIII length				
Full-length rFVIII	1	31/98	NA	NA
B-domain deleted rFVIII	1	44/60	NA	NA
EHL	3	136/224	56.8% (21.9%; 88.4%)	0.099

Notes: SHL, standard half-life; EHL, extended half-life; PUPs, previously untreated patients; PTPs, previously treated patients; FVIII, factor VIII; rFVIII, recombinant FVIII; CI, confidence interval; τ^2 , Tau², between-study variance; N, the number of studies included in the analysis; NA, not available.