**Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and subgroup analyses of the intra-patient comparison of the HAVEN 3 trial**

# Supplementary material

## Methods: SLR

### Supplementary Table 1. Summary protocol of the May 2018 SLR.

|  |  |
| --- | --- |
| **Objectives and research questions** | |
| Project objective | The overall objective of this SLR update is to provide recent information (post-December 2016) on clinical efficacy, health-related quality of life and safety from clinical trials and registries of pharmacological treatments used in mild, moderate and severe hemophilia A (with specific focus on the non-inhibitor population only). |
| **Studies to include** | |
| Study designs | Inclusion criteria   * Any interventional trial, phase 2 and beyond * All controlled and uncontrolled studies, including RCTs, single arms studies, or open-label trials * Non-interventional: registries, PMS, PASS   Exclusion criteria   * Non-interventional trials (with the exception of registries, PMS, PASS) * Observational studies * Cohort studies * Retrospective studies * Database/patient record analyses, chart reviews * Case reports, case series * Cross-sectional study * Reviews, comments, letters, editorials |
| Population | Inclusion criteria   * Patients of all ages with mild, moderate or severe hemophilia A without inhibitors   Exclusion criteria   * Acquired hemophilia * Selected sub-populations, e.g. undergoing surgery, undergoing knee replacement, hemarthroses, dental extraction, circumcision, pregnancy, etc. |
| Interventions | Inclusion criteria   * Studies assessing any pharmacological intervention (licensed and pipeline) for the treatment of hemophilia A   Exclusion criteria   * Non-pharmacological interventions * Herbal non-blood preparation * Drugs no longer on market:   + FVIII-P   + Konyne, Proplex (Prothrombincomplex concentrates)   + Tranexamic acid   + Epsilon-aminocaproic Acid   + Danazol   + Hyate:C (Porcine FVIII concentrate) |
| Comparator | * Studies comparing pharmacological interventions either to each other or to placebo or standard of care were included. * Studies assessing interventions of interest without any comparator group (single-arm studies) were also included. |
| Language | * English language only |
| **Data sources** | |
| Databases | * Medical Literature Analysis and Retrieval System Online [MEDLINE®] * Excerpta Medica DataBASE [Embase®] * Cochrane Central databases   + Cochrane Central Register of Controlled Trials (CENTRAL)   + Cochrane Database of Systematic Reviews (CDSR)   + Database of Abstracts of Reviews of Effects (DARE)   + Health technology assessment (HTA) database |
| Other sources | * Conference searching (2017-2018)   + World Federation of Haemophilia (WFH): World Congress 2016   + International Society of Thrombosis and Haemostasis (ISTH)   + International Conference on Thrombosis, Bleeding Disorders and Hemostasis (ICTBDH)   + American Society of Hematology (ASH)   + National Haemophilia Foundation (NHF): Annual Meeting   + European Haemophilia Consortium (EHC): Annual Conference   + European Association of Haemophilia and Allied Disorders (EAHAD): Annual Congress   + Haemophilia Foundation Australia: Australian and New Zealand Haemophilia Conference * Bibliography |

Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System.

FVIII, factor VIII; PASS, post-authorization safety studies; PMS, post-marketing surveillance; RCT, randomized controlled trial; SLR, systematic literature review.

### Supplementary Table 2. Final search strategy for Embase/MEDLINE (using Embase.com), for May 2018 SLR.

| No. | Query | Results |
| --- | --- | --- |
| #1 | 'hemophilia a'/exp | 20707 |
| #2 | 'hemophilia a':ab,ti OR 'haemophilia a':ab,ti OR 'hemophilia type a':ab,ti OR 'haemophilia type a':ab,ti | 12934 |
| #3 | 'classical hemophilia':ab,ti OR 'classical haemophilia':ab,ti OR 'classic hemophilia':ab,ti OR 'classic haemophilia':ab,ti | 259 |
| #4 | ('factor viii' NEAR/4 deficienc\*):ab,ti | 1126 |
| #5 | ('factor 8' NEAR/4 deficienc\*):ab,ti | 23 |
| #6 | hemophilia:ti OR haemophilia:ti NOT ('hemophilia b':ti OR 'haemophilia b':ti) | 16274 |
| #7 | hemophiliacs:ti OR haemophiliacs:ti OR 'hemophiliac patients':ti OR 'haemophiliac patients':ti | 1610 |
| #8 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 | 27686 |
| #9 | 'hemophilia'/exp/dm\_dt | 7112 |
| #10 | 'blood clotting factor 8'/exp OR 'recombinant blood clotting factor 8'/exp | 26324 |
| #11 | 'blood clotting factor 8 concentrate'/exp | 2720 |
| #12 | immunate\*:ab,ti,tn OR optivate\*:ab,ti,tn OR haemoctin\*:ab,ti,tn OR beriate\*:ab,ti,tn OR (haemate NEXT/1 p):ab,ti,tn OR octanate\*:ab,ti,tn OR wilate\*:ab,ti,tn OR recombinate\*:ab,ti,tn OR factane\*:ab,ti,tn OR emoclot\*:ab,ti,tn | 1182 |
| #13 | fanhdi\*:ab,ti,tn OR wilnativ\*:ab,ti,tn OR octafil\*:ab,ti,tn OR amofil\*:ab,ti,tn OR humaclot\*:ab,ti,tn OR talate\*:ab,ti,tn OR alphanate\*:ab,ti,tn OR emowil\*:ab,ti,tn OR klott\*:ab,ti,tn OR aafact\*:ab,ti,tn OR bioclate\*:ab,ti,tn OR biostate\*:ab,ti,tn OR wilate\*:ab,ti,tn | 448 |
| #14 | helixate\*:ab,ti,tn OR iblias\*:ab,ti,tn OR kogenate\*:ab,ti,tn OR kovaltry\*:ab,ti,tn OR novoeight\*:ab,ti,tn OR zonovate\*:ab,ti,tn OR refacto\*:ab,ti,tn OR advate\*:ab,ti,tn | 1601 |
| #15 | elocta\*:ab,ti,tn OR nuwiq\*:ab,ti,tn OR obizur\*:ab,ti,tn OR voncento\*:ab,ti,tn OR adynovate\*:ab,ti,tn OR factyla\*:ab,ti,tn OR adynovi\*:ab,ti,tn OR recombinate\*:ab,ti,tn OR xyntha\*:ab,ti,tn OR greengene\*:ab,ti,tn | 948 |
| #16 | 'octocog alfa':ab,ti,tn OR (turoctocog NEXT/1 alfa\*):ab,ti,tn OR 'moroctocog alfa':ab,ti,tn OR 'efmoroctocog alfa':ab,ti,tn OR 'simoctocog alfa':ab,ti,tn OR 'efraloctocog alfa':ab,ti,tn OR 'susoctocog alfa':ab,ti,tn | 241 |
| #17 | '139076-62-3':rn OR '1192451-26-5':rn OR '1270012-79-7':rn OR '1219013-68-9':rn OR '284036-24-4':rn OR '1456622-91-5':rn OR '1339940-90-7':rn | 1438 |
| #18 | 'pf-06741086':ab,ti,tn OR 'bay w 6240':ab,ti,tn OR nn7008:ab,ti,tn OR 'nn 7008':ab,ti,tn OR 'bay 81-8973':ab,ti,tn OR 'bay 818973':ab,ti,tn OR 'bay81-8973':ab,ti,tn OR 'pf-05208756':ab,ti,tn OR 'pf-5208756':ab,ti,tn OR '2pf-05280602':ab,ti,tn | 53 |
| #19 | 'bax 855':ab,ti,tn OR bax855:ab,ti,tn OR 'bax 802':ab,ti,tn OR bax802:ab,ti,tn OR 'bay 94-9027':ab,ti,tn OR 'bay94-9027':ab,ti,tn OR 'bay 949027':ab,ti,tn OR 'bay 14-2222':ab,ti,tn OR 'bay14-2222':ab,ti,tn OR 'bay 142222':ab,ti,tn OR 'bay79-4980':ab,ti,tn OR 'bay 79-4980':ab,ti,tn OR 'bay 794980':ab,ti,tn | 182 |
| #20 | rfviiifc:ab,ti,tn OR bddrfviii:ab,ti,tn OR sct800:ab,ti,tn OR 'sct 800':ab,ti,tn OR 'obi-1':ab,ti,tn OR 'bmn 270':ab,ti,tn OR bmn270:ab,ti,tn OR 'bax 826':ab,ti,tn OR bax826:ab,ti,tn OR 'bay79-4980':ab,ti,tn OR 'bay 79-4980':ab,ti,tn OR 'bay794980':ab,ti,tn OR biib031:ab,ti,tn OR 'biib 031':ab,ti,tn | 316 |
| #21 | 'factor viii':ab,ti OR fviii:ab,ti OR 'factor 8':ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR treated:ab,ti OR regimen\*:ab,ti OR concentrate\*:ab,ti OR recombinant:ab,ti OR dose\*:ab,ti OR dosing:ab,ti OR prophylaxis:ab,ti OR prophylactic:ab,ti OR agent\*:ab,ti OR medication\*:ab,ti OR infusion\*:ab,ti OR (adverse NEXT/2 effect\*):ab,ti OR complication\*:ab,ti OR 'plasma-derived':ab,ti) | 15908 |
| #22 | 'factor viii product':ab,ti OR 'fviii product':ab,ti OR 'factor 8 product' | 322 |
| #23 | 'recombinant factor viii':ab,ti OR 'recombinant fviii':ab,ti OR 'recombinant factor 8' | 1906 |
| #24 | rfviii:ab,ti OR 'r-fviii':ab,ti OR rhfviii:ab,ti | 1217 |
| #25 | (antihemophilic NEXT/1 factor\*):ab,ti OR (antihaemophilic NEXT/1 factor\*):ab,ti OR (anti NEXT/1 hemophilic NEXT/1 factor\*):ab,ti OR (anti NEXT/1 haemophilic NEXT/1 factor\*):ab,ti | 686 |
| #26 | 'desmopressin'/exp | 11126 |
| #27 | desmopressin:ab,ti,tn OR ddavp:ab,ti,tn OR minirin\*:ab,ti,tn | 6583 |
| #28 | 'tranexamic acid'/exp OR 'tranexamic acid':ab,ti,tn | 10907 |
| #29 | 'aminocaproic acid'/exp OR 'aminocaproid acid':ab,ti,tn | 6039 |
| #30 | 'emicizumab'/exp | 104 |
| #31 | emicizumab\*:ab,ti,tn | 60 |
| #32 | ace910:ab,ti,tn OR 'ace 910':ab,ti,tn OR rg6013:ab,ti,tn OR 'rg 6013':ab,ti,tn OR 'ro 5534262':ab,ti,tn OR ro5534262:ab,ti,tn OR 'ro 553-4262':ab,ti,tn | 78 |
| #33 | '1610943-06-0':rn | 89 |
| #34 | 'hemostatic agent'/de | 9132 |
| #35 | 'factor replacement':ab,ti | 1018 |
| #36 | 'eptacog alfa':ab,ti,tn OR 'nn-007':ab,ti,tn OR nn007:ab,ti,tn OR 'nn 1731':ab,ti,tn OR nn1731:ab,ti,tn OR 'bay86-6150':ab,ti,tn OR 'bay 86-6150':ab,ti,tn OR 'bay 866150':ab,ti,tn OR 'vatreptacog alfa':ab,ti,tn OR novoseven\*:ab,ti,tn OR niastase\*:ab,ti,tn | 2288 |
| #37 | 'blood clotting factor 7a inhibitor'/exp OR 'recombinant blood clotting factor 8'/exp | 3863 |
| #38 | 'factor 7a':ab,ti OR 'factor viia':ab,ti OR fviia:ab,ti OR rfviia:ab,ti | 6711 |
| #39 | 'bax 817':ab,ti,tn OR bax817:ab,ti,tn | 5 |
| #40 | 'activated prothrombin complex'/exp | 2000 |
| #41 | feiba:ab,ti,tn | 1162 |
| #42 | 'anti-inhibitor coagulant complex':ab,ti OR 'aicc complex':ab,ti | 48 |
| #43 | (activated NEXT/1 prothrombin NEXT/1 complex NEXT/1 concentrate\*):ab,ti | 655 |
| #44 | 'csl 689':ab,ti,tn OR csl689:ab,ti,tn | 3 |
| #45 | iti:ab,ti | 2035 |
| #46 | 'immune tolerance induction':ab,ti | 888 |
| #47 | 'n8-gp':ab,ti,tn OR 'nn 7088':ab,ti,tn OR nn7088;ab,ti,tn | 52 |
| #48 | afstyla\*:ab,ti,tn | 20 |
| #49 | 'lonoctocog alfa':ab,ti,tn | 4 |
| #50 | '1388129-63-2':rn | 820 |
| #51 | 'csl 627':ab,ti,tn OR cls627:ab,ti,tn | 8 |
| #52 | 'aln-at3':ab,ti,tn OR 'aln-at3sc':ab,ti,tn OR fitusiran:ab,ti,tn OR alnylam\*:ab,ti,tn | 77 |
| #53 | #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 | 74389 |
| #54 | 'clinical trial'/de | 961647 |
| #55 | 'randomized controlled trial'/de | 492444 |
| #56 | 'placebo'/de | 321569 |
| #57 | rct:ab,ti OR random\*:ab,ti | 1282122 |
| #58 | ((single OR double) NEXT/1 (blind\* OR mask\*)):ab,ti AND (trial\*:ab,ti OR study:ab,ti OR rct:ab,ti OR cct:ab,ti) | 193864 |
| #59 | ((treble OR triple) NEXT/1 (blind\* OR mask\*)):ab,ti AND (trial\*:ab,ti OR study:ab,ti OR rct:ab,ti OR cct:ab,ti) | 820 |
| #60 | placebo\*:ab,ti | 269053 |
| #61 | (single NEXT/2 arm\*):de,ab,ti AND (trial\*:ab,ti OR study:ab,ti OR rct:ab,ti OR cct:ab,ti) | 10828 |
| #62 | ('non-randomized' NEAR/3 (trial\* OR study OR design)):ab,ti OR ('non-randomised' NEAR/3 (trial\* OR study OR design)):ab,ti | 9600 |
| #63 | 'non-rct':ab,ti OR nrct:ab,ti | 336 |
| #64 | (uncontrolled NEAR/3 (trial\* OR study OR design)):ab,ti OR ('non-controlled' NEAR/3 (trial\* OR study OR design)):ab,ti | 5192 |
| #65 | 'controlled clinical trial':de | 433742 |
| #66 | (controlled NEAR/3 (trial\* OR study)):ab,ti | 363315 |
| #67 | (parallel NEXT/1 group\*):ab,ti | 21248 |
| #68 | 'clinical trial'/de | 961647 |
| #69 | 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp | 95370 |
| #70 | ('phase 2' NEAR/3 (trial\* OR study OR design)):ab,ti | 12453 |
| #71 | ('phase ii' NEAR/3 (trial\* OR study OR design)):ab,ti | 51902 |
| #72 | ('phase 3' NEAR/3 (trial\* OR study OR design)):ab,ti | 15528 |
| #73 | ('phase iii' NEAR/3 (trial\* OR study OR design)):ab,ti | 36790 |
| #74 | ('phase 4' NEAR/3 (trial\* OR study OR design)):ab,ti | 521 |
| #75 | ('phase iv' NEAR/3 (trial\* OR study OR design)):ab,ti | 1446 |
| #76 | 'open label':de,ab,ti | 62734 |
| #77 | (open NEXT/3 (trial\* OR study OR design)):ab,ti | 45783 |
| #78 | crossover:de,ab,ti OR 'cross-over':de,ab,ti | 101142 |
| #79 | 'postmarketing surveillance'/exp OR 'post-marketing':ab,ti OR postmarketing:ab,ti | 36469 |
| #80 | #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 | 2329973 |
| #81 | #80 NOT ('animal'/de NOT 'human'/exp) | 2283368 |
| #82 | 'disease registry'/exp | 11070 |
| #83 | 'register'/exp | 107868 |
| #84 | registry:ab,ti OR registries:ab,ti OR register\*:ab,ti | 359224 |
| #85 | (hemophilia NEXT/2 database):ab,ti OR (haemophilia NEXT/2 database):ab,ti | 79 |
| #86 | #82 OR #83 OR #84 OR #85 | 374222 |
| #87 | #80 OR #86 | 2616766 |
| #88 | #8 AND #53 | 16236 |
| #89 | #87 AND #88 | 2601 |
| #90 | #87 AND #88 AND [14-12-2016]/sd NOT [9-5-2018]/sd | **439** |

Searches were run from 13th Dec 2016 to 14th May 2018.

### Supplementary Table 3. Final search strategy for Cochrane (using Cochrane interface) for May 2018 systematic literature review.

| No. | Query | Results |
| --- | --- | --- |
| #1 | [mh "hemophilia a"] | 227 |
| #2 | "hemophilia a":ab,ti or "haemophilia a":ab,ti,kw or "hemophilia type a":ab,ti or "haemophilia type a":ab,ti,kw | 509 |
| #3 | "classical hemophilia":ab,ti,kw or "classical haemophilia":ab,ti,kw or "classic hemophilia":ab,ti,kw or "classic haemophilia":ab,ti,kw | 0 |
| #4 | ("factor viii" near/4 deficienc\*):ab,ti,kw | 17 |
| #5 | ("factor 8" near/4 deficienc\*):ab,ti,kw | 0 |
| #6 | (hemophilia:ti or haemophilia:ti) not ("hemophilia b":ti or "haemophilia b":ti) | 563 |
| #7 | "hemophiliacs":ti,kw or "haemophiliacs":ti,kw or "hemophiliac patients":ti,kw or " haemophiliac patients":ti,kw | 70 |
| #8 | [1-#7] | 793 |
| #9 | [mh "hemophilia a"/DT] or [mh "hemophilia a"/PC] or [mh "hemophilia a"/TH] | 209 |
| #10 | [mh "factor viii"] | 317 |
| #11 | immunate\*:ab,ti,kw or optivate\*:ab,ti,kw or haemoctin\*:ab,ti,kw or beriate\*:ab,ti,kw or (haemate next/1 p):ab,ti,kw or octanate\*:ab,ti,kw or wilate\*:ab,ti,kw or recombinate\*:ab,ti,kw or factane\*:ab,ti,kw or emoclot\*:ab,ti,kw | 31 |
| #12 | fanhdi\*:ab,ti,kw or wilnativ\*:ab,ti,kw or octafil\*:ab,ti,kw or amofil\*:ab,ti,kw or humaclot\*:ab,ti,kw or talate\*:ab,ti,kw or alphanate\*:ab,ti,kw or emowil\*:ab,ti,kw or klott\*:ab,ti,kw or aafact\*:ab,ti,kw or bioclate\*:ab,ti,kw or biostate\*:ab,ti,kw or wilate\*:ab,ti,kw | 12 |
| #13 | helixate\*:ab,ti,kw or iblias\*:ab,ti,kw or kogenate\*:ab,ti,kw or kovaltry\*:ab,ti,kw or novoeight\*:ab,ti,kw or zonovate\*:ab,ti,kw or refacto\*:ab,ti,kw or advate\*:ab,ti,kw or elocta\*:ab,ti,kw or nuwiq\*:ab,ti,kw | 60 |
| #14 | obizur\*:ab,ti,kw or voncento\*:ab,ti,kw or adynovate\*:ab,ti,kw or factyla\*:ab,ti,kw or adynovi\*:ab,ti,kw or xyntha\*:ab,ti,kw or greengene\*:ab,ti,kw | 19 |
| #15 | "octocog alfa":ab,ti,kw or (turoctocog next/1 alfa\*):ab,ti,kw or "moroctocog alfa":ab,ti,kw or "efmoroctocog alfa":ab,ti,kw or "simoctocog alfa":ab,ti,kw or "efraloctocog alfa":ab,ti,kw | 20 |
| #16 | "pf-06741086":ab,ti,kw or "bay w 6240":ab,ti,kw or "nn 7008":ab,ti,kw or nn7008:ab,ti,kw or "bay 81-8973":ab,ti,kw or "pf-05208756":ab,ti,kw or "pf-5208756":ab,ti,kw or "2pf-05280602":ab,ti,kw | 30 |
| #17 | "bax 855":ab,ti,kw or bax855:ab,ti,kw or bax802:ab,ti,kw or "bax 802":ab,ti,kw or "bay94-9027":ab,ti,kw or "bay 94-9027":ab,ti,kw or "bay 949027":ab,ti,kw or "bay 14-2222":ab,ti,kw or "bay14-2222":ab,ti,kw or "bay 142222":ab,ti,kw or "bay79-4980":ab,ti,kw or "bay 79-4980":ab,ti,kw or "bay 794980":ab,ti,kw | 34 |
| #18 | rfviiifc:ab,ti,kw or bddrfviii:ab,ti,kw or sct800:ab,ti,kw "sct 800":ab,ti,kw or "obi-1":ab,ti,kw or "bmn 270":ab,ti,kw or bmn270:ab,ti,kw or "bax 826":ab,ti,kw or bax826:ab,ti,kw or "bay79-4980":ab,ti,kw or "bay 79-4980":ab,ti,kw or "bay 794980":ab,ti,kw or biib031:ab,ti,kw or "biib 031":ab,ti,kw | 32 |
| #19 | "factor viii":ab,ti,kw or "fviii":ab,ti,kw or "factor 8":ab,ti,kw | 938 |
| #20 | rfviii:ab,ti,kw or "r-fviii":ab,ti,kw or rhfviii:ab,ti,kw | 94 |
| #21 | "blood clotting factor 8":ab,ti,kw or "recombinant blood clotting factor 8":ab,ti,kw | 335 |
| #22 | (antihemophilic next/1 factor\*):ab,ti or (antihaemophilic next/1 factor\*):ab,ti or (anti next/1 hemophilic next/1 factor\*):ab,ti or (anti next/1 haemophilic next/1 factor\*):ab,ti | 21 |
| #23 | [mh "deamino arginine vasopressin"] | 345 |
| #24 | desmopressin:ab,ti,kw or ddavp:ab,ti,kw | 655 |
| #25 | [mh "tranexamic acid"] or "tranexamic acid":ab,ti,kw | 1542 |
| #26 | [mh "aminocaproic acid"] or "aminocaproic acid":ab,ti,kw | 238 |
| #27 | [mh "antifibrinolytic agents"] | 647 |
| #28 | "emicizumab":ab,ti,kw | 14 |
| #29 | ace910:ab,ti,kw or "ace 910":ab,ti,kw or rg6013:ab,ti,kw or "rg 6013":ab,ti,kw or "ro 5534262":ab,ti,kw or ro5534262:ab,ti,kw or "ro 553-4262":ab,ti,kw | 9 |
| #30 | [mh "blood coagulation factors"/TU] | 2344 |
| #31 | [mh ^coagulants] | 72 |
| #32 | "factor replacement":ab,ti | 26 |
| #33 | "eptacog alfa":ab,ti,kw or "nn-007":ab,ti,kw or nn007:ab,ti,kw or "nn 1731":ab,ti,kw or nn1731:ab,ti,kw or "bay86-6150":ab,ti,kw or "bay 86-6150":ab,ti,kw or "bay 866150":ab,ti,kw or "vatreptacog alfa":ab,ti,kw or novoseven\*:ab,ti,kw or niastase\*:ab,ti,kw | 90 |
| #34 | [mh "factor VIIa"] | 210 |
| #35 | "factor 7a":ab,ti or "factor viia":ab,ti or fviia:ab,ti or rfviia:ab,ti | 333 |
| #36 | "bax 817":ab,ti,kw or bax817:ab,ti,kw | 0 |
| #37 | Feiba:ab,ti,kw | 44 |
| #38 | "anti-inhibitor coagulant complex":ab,ti,kw or "anti-inhibitor coagulant complex":ab,ti,kw or "aicc complex":ab,ti,kw | 13 |
| #39 | (activated next/1 prothrombin next/1 complex next/1 concentrate\*):ab,ti,kw | 26 |
| #40 | "csl 689":ab,ti,kw or csl689:ab,ti,kw | 0 |
| #41 | iti:ab,ti | 113 |
| #42 | "immune tolerance induction":ab,ti | 25 |
| #43 | "n8-gp":ab,ti,kw or nn7088:ab,ti,kw or "nn 7088":ab,ti,kw | 4 |
| #44 | afstyla\*:ab,ti,kw | 1 |
| #45 | "lonoctocog alfa":ab,ti,kw | 0 |
| #46 | "csl 627":ab,ti,kw or cls627:ab,ti,kw | 0 |
| #47 | "aln-at3":ab,ti,kw or "aln-at3sc":ab,ti,kw or fitusiran:ab,ti,kw or alnylam\*:ab,ti,kw | 11 |
| #48 | [2-#47] | 6015 |
| #49 | #8 and #48 | 578 |
| #50 | #49 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Technology Assessments | 543 |
| #51 | #50 Publication Year from 2017 to 2018, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Technology Assessments | **68** |

Searches were run from 13th Dec 2016 to 14th May 2018.

### Supplementary Text 1. Assessment of risk of bias of included trials.

Four studies included in the network meta-analysis (NMA) were RCTs and were assessed according to the National Institute for Health and Care Excellence (NICE) Critical Appraisal Checklist for RCTs. These four studies were LEOPOLD 2, A-LONG, SPINART, and HAVEN 3 (Supplementary Table 4).

One of the studies included in a sensitivity analysis of this NMA (Valentino 2012) was a single arm study with within-trial comparison and was therefore assessed according to the National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies (Supplementary Table 5).

Overall these assessments found that all RCTs carried at least some risk of bias according to NICE criteria, most notably the risk introduced by lack of blinding. HAVEN 3 in particular, but also LEOPOLD 2 and SPINART stood out for showing low risk of bias for most of the categories assessed. The NIH Quality Assessment Tool showed an overall fair to good quality rating on the single arm study—though this remains a single arm study.

### Supplementary Table 4. NICE critical appraisal of studies included in NMA.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Study acronym or NCT number** | **Was randomization carried out appropriately?** | **Was the concealment of treatment allocation adequate?** | **Were the groups similar at the outset of the study in terms of prognostic factors?** | **Were the care providers, participants and outcome assessors blind to treatment allocation?** | **Were there any unexpected imbalances in drop-outs between groups?** | **Is there any evidence to suggest that the authors measured more outcomes than they reported?** | **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?** |
|
| Mahlangu 2018  (published after  the SLR update read out) | HAVEN3; NCT02847637 |  |  |  |  |  |  |  |
| Kavakli 2015,  Fujii 2016 | LEOPOLD 2; NCT01233258 |  |  |  |  |  |  |  |
| Mahlangu 2014 | A-LONG; NCT01181128 |  |  |  |  |  |  |  |
| Manco-Johnson 2013 | SPINART, NCT00623480 |  |  |  |  |  |  |  |

Key: Green, low risk; red, high risk; orange, not clear.

NCT, National Clinical Trial; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis.

Source: NICE [3]

Supplementary Table 5. NIH critical appraisal of case series studies (or single arm studies).  
A: Questions 1 to 5

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Study acronym or NCT number** | **1. Was the study question or objective clearly stated?** | | **2. Was the study population clearly and fully described, including a case definition?** | | **3. Were the cases consecutive?** | | **4. Were the subjects comparable?** | | **5. Was the intervention clearly described?** | |
| **Yes, No, Other (CD, cannot determine; NA, not applicable;  NR, not reported)** | **Justification** | **Yes, No, Other (CD, cannot determine; NA, not applicable;  NR, not reported)** | **Justification** | **Yes, No, Other (CD, cannot determine; NA, not applicable;  NR, not reported)** | **Justification** | **Yes, No, Other (CD, cannot determine; NA, not applicable;  NR, not reported)** | **Justification** | **Yes, No, Other (CD, cannot determine; NA, not applicable;  NR, not reported)** | **Justification** |
| Valentino 2012 | NCT00243386 | Yes | Objective is clearly stated | Yes | Inclusion criteria and subjects’ characteristics clearly explained | CD |  | Yes |  | Yes | Dose and dose adjustments explained |

B: Questions 6 to 9

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Study acronym or NCT number** | **6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?** | | **7. Was the length of follow-up adequate?** | | **8. Were the statistical methods well-described?** | | **9. Were the results well-described?** | | **Quality rating** | |
| **Yes, No, Other (CD, NA, NR)** | **Justification** | **Yes, No, Other (Other (CD, NA, NR)** | **Justification** | **Yes, No, Other (Other (CD, NA, NR)** | **Justification** | **Yes, No, Other (Other (CD, NA, NR)** | **Justification** | **Good, Fair, Poor** | **If POOR, please state why** |
| Valentino 2012 | NCT00243386 | Yes | Mean annualized bleeding rates, median annualized bleeding rates | Yes | On-demand: 6 months Prophylactic: 12 months | Yes | Median differences of ABRs and percentage reductions of ABRs between treatment regimens were evaluated using the non-parametric Wilcoxon s signed-rank test with each test performed at a 5% alpha level and adjusted for multiple testing (0.05 ‚ number of tests), with no P-value > 0.01 considered statistically significant. The comparisons between on-demand and prophylaxis were paired as each subject was first treated on-demand and then on prophylaxis. | Yes | Mean annualized bleeding rates, median annualized bleeding rates, hemostatic efficacy/ratings well explained | Good |  |

CD, cannot determine; NA, not applicable; NCT, National Clinical Trial; NIH, National Institutes of Health; NR, not reported

Source: NIH [4]

## Methods: NMA

### Supplementary Text 2. Outcome of interest for the NMA.

The patient, intervention, comparator, outcome- (PICO)-based search criteria used in the SLR were broad. However, for the NMA, only one major efficacy outcome was considered of interest in the first instance, based on its importance in hemophilia A: total treated bleeds.

Bleeding events are common primary endpoints in studies in Hemophilia A, based on bleeding being the main clinical symptom in individuals with the disease [5]. Bleeding and its complications negatively affect the quality of life of individuals with Hemophilia A. The model inputs for bleeding events are provided in Supplementary Table 6.

Our model used the assumption that the outcomes were defined in the same way across all studies. However, the definition and reporting of a “bleed” is likely to have differed between studies [5]. Bleeding events are generally reported by patients, and there is no agreed standard regarding the definition and reporting of bleeding outcomes. There are substantial differences in how bleeding frequency is measured and reported in studies. In studies with very short follow-up periods, measurement of events may have been inaccurate if the bleeding frequency was low or was affected by seasonal variation.

Beyond the definition of a bleed itself, one must also account for the variation in each bleeding episode’s treatment. This appeared as more or less clear in the different included studies (Supplementary Table 7), and we have therefore run a sensitivity analysis to address this point.

### Supplementary Table 6. Input data to the NMA models.

| **Trial ID** | **Source publication** | **Treatment** | **Variable** | **Value** | **Detailed calculation (where available)** | **Variables modelled in the NMA** |
| --- | --- | --- | --- | --- | --- | --- |
| A-LONG |  | FVIII prophylaxis | exposure | 12.38 | (23\*28)/52 | x |
| Shapiro 2017, Table 1 | nbleeds | 92.00 |  | x |
| Shapiro 2017 | npat | 23 |  |  |
| Mahlangu 2014 | durcontrolperiod | 28 |  |  |
|  | On-demand FVIII | exposure | 12.78 | (23\*28.9)/52 | x |
| Shapiro 2017, Table 1 | nbleeds | 456.00 |  | x |
| Shapiro 2017 | npat | 23 |  |  |
| Mahlangu 2014 | durcontrolperiod | 28.9 |  |  |
| HAVEN 3 | From IPD [6] | Emicizumab prophylaxis QW | exposure | 22.10 |  | x |
| nbleeds | 37.00 |  | x |
| Emicizumab prophylaxis Q2W | exposure | 22.30 |  | x |
| nbleeds | 32.00 |  | x |
| On-demand FVIII | exposure | 8.18 |  | x |
| nbleeds | 369.00 |  | x |
| LEOPOLD2 | Kavakli 2015 [7] | FVIII prophylaxis | exposure | 59.00 | (59\*52)/52 | x |
| nbleeds | 293.00 |  | x |
| npat | 59 |  |  |
| durcontrolperiod | 52 |  |  |
| On-demand FVIII | exposure | 21.00 | (21\*52)/52 | x |
| nbleeds | 1204.00 |  | x |
| npat | 21 |  |  |
| durcontrolperiod | 52 |  |  |
| SPINART | Manco-Johnson 2017 [8] | FVIII prophylaxis | exposure | 127.44 | (42\*157.79)/52 | x |
| nbleeds | 264.00 |  | x |
| npat | 42 |  |  |
| durcontrolperiod | 157.79 | 1104.5/7 |  |
| On-demand FVIII | exposure | 126.58 | (42\*156.71)/52 | x |
| nbleeds | 4338.00 |  | x |
| npat | 42 |  |  |
| durcontrolperiod | 156.71 | 1097/7 |  |
| Valentino 2012 | Valentino 2012 [9] | FVIII prophylaxis | exposure | 31.68 | 11571/365.25 | x |
| nbleeds | 104.00 |  | x |
| On-demand FVIII | exposure | 33.51 | 12241/365.25 | x |
| nbleeds | 1640 |  | x |

Base case and SA1 (fixed effect) includes: A-LONG, HAVEN3, LEOPOLD II, SPINART

SA2 (including only trials reporting known treated bleeds) includes: A-LONG, HAVEN3, SPINART

SA3 (including single arm trial in addition to base case) includes: A-LONG, HAVEN3, LEOPOLD II, SPINART, Valentino et al 2012

Exposure (in patient years): ((number of patients (npat) \* duration of controlled period in weeks (durcontrolperiod))/52 weeks)

durcontrolperiod, duration of controlled period (in weeks); IPD, individual patient data from HAVEN 3; nbleeds, number of bleeds; npat, number of patients; SA, sensitivity analysis.

### *Supplementary Table 7. Definitions of total treated bleeds*.

|  |  |  |
| --- | --- | --- |
| **Trials** | **Definition as written in source publication** | **Clear or unclear** |
| A‑LONG | A standardized definition of a bleeding episode was used in this study. A bleeding episode started from the first sign of bleeding and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Any injection to treat the bleeding episode, more than 72 hours after the preceding one, was considered the first injection to treat a new bleeding episode at the same location. Any bleeding at a different location was considered a separate bleeding episode regardless of time from last injection. This definition has been proposed by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis, and has been used by the PedNet multicenter study in hemophilia.[10,11] | clear |
| HAVEN 3 | **treated bleeds**: all bleeds followed directly by a "treatment for bleed", irrespective of the time between the treatment and the preceding bleed. Bleeds due to surgery/procedure are excluded. Two bleeds of the same type (e.g., “joint,” “muscle,” or “other”) and at the same anatomical location were considered to be one bleed if the second occurred within 72 hours from the last treatment for the first bleed (“72 hour rule”).  **all bleeds:** number of bleeds in the database (including surgery/procedure, 72-hour rule not implemented) (Roche data on File, HAVEN3). | clear |
| LEOPOLD 2 | No clear definition of a bleed located.[12] | unclear |
| SPINART | “A BE [bleeding episode] was defined as any episode of external bleeding (i.e, epistaxis), bruising, pain or limited function for which FVIII was infused. A joint BE (subset of total BEs) was defined as an event with pain, swelling, tingling, warmth or limited motion of an extremity for which FVIII was infused.”[8] | clear |
| Valentino 2012 | No clear definition of a bleed located[9] | unclear |

## Methods: Subgroup analysis of the intra-patient comparison of the HAVEN 3 trial

### Supplementary Text 3. Algorithms for selecting patients for the European label group.

The European label group was used for the German benefit assessment of emicizumab (Hemlibra®) and was comprised a patient population selected according to the following inclusion criteria and algorithms:

1. Patients were ‘in-label’.
   1. Use prescription information to calculate weekly dose (same for all weeks).
   2. For short acting factor VIII (FVIII; Advate® [13], Kovaltry® [14], Kogenate® [15], NovoEight® [16], ReFacto AF® [17]), patient was in-label if total weekly prescribed dose was at least 47 IU/kg and no more than 140 IU/kg.
   3. For long acting FVIII (Elocta/Eloctate® [18]), patient is in-label if total weekly prescribed dose at least 35 IU/kg and no more than 152 IU/kg
2. Weekly dose in-label at least 80% of weeks.
   1. Calculate daily dose per kg for each patient if data are missing.
   2. Derive week number.
   3. Get the total weekly dose for each week using points a) and b).
   4. Check each week – for short-acting FVIII, if total weekly dose was at least 47 IU/kg then week was in-label. For long-acting FVIII, if total weekly dose was at least 35 IU/kg then week was in-label.
   5. Calculate percentage of weeks in label.
   6. Flag patients with ≥ 80% weeks in label.
3. At least 80% of weeks with no treatment interruptions.
   1. Calculate the difference in days between each dosing.
   2. Week was considered to have a treatment interruption if difference in days:
      1. (a) was more than 3 days for short-acting FVIII and more than 5 days for long-acting FVIII within the week
      2. (a) was more than 3 days or more than 5 days in the beginning of the week (no dose in the first 3 or 5 days)
      3. (a) was more than 3 days or more than 5 days in the end of the week (no dose in the last 3 or 5 days)
      4. interruption happened between weeks and no dose on the first day of second week
      5. there were 2 or 4 days with no dosing during the first week
      6. no doses occurred during the week.

## Results: SLR

### Supplementary Figure 1. PRISMA flow chart of study selection process.



Searches include an original SLR (run in December 2016) and an SLR update (run in May 2018).

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

## Results: NMA

### Supplementary Figure 2. Flow diagram of studies included in NMA.



The study by Valentino *et al*. was included in SA3; the four remaining studies were included in the base-case NMA and in SA1 and SA2.

NMA, network meta-analysis; SA, sensitivity analysis; SLR, systematic literature review.

### Supplementary Text 4. Selection of trials for the NMA.

94 studies were identified in the SLR targeting Hemophilia A adults without inhibitors, but only four studies (five including HAVEN 3) were included in this NMA. For one study (A-LONG) only part was randomized and only this part was considered. We were only interested in comparisons of prophylaxis versus on demand/no prophylaxis. Further, NMA methodology requires the use of randomized data, i.e. relative effect summary information with no or limited unknown or unmeasured bias or confounding due to treatment allocation. These criteria alone excluded 74 single arms studies, non-randomized studies and observational studies, or post-marketing surveillance studies from eligibility.

As we are only interested in comparisons of prophylaxis versus on demand/no prophylaxis, Arm D from HAVEN 3 does not qualify for inclusion. We also excluded studies in pediatric populations in order to ensure that the trials included in our NMA would match our HAVEN 3 trial target population as closely as possible. As such another 11 studies were excluded (32 studies of the 94 were in children).

One exception was made to the rule about including only relative effects extracted from randomized trials in our NMA for one of the sensitivity analyses. Indeed, Valentino et al. 2012 [19] is a longitudinal, non-randomized, cross-over comparison and provides an effect estimate of on demand and prophylaxis treatments on Advate. Each subject was first treated on-demand for 6 months and then on prophylaxis for 12 months, and statistical comparisons between these regimens were paired. While not as robust as evidence coming from a well conducted RCT, the gold standard in terms of unbiased evidence—each subject was first treated on-demand and then on prophylaxis, and the comparisons between on-demand and prophylaxis were paired. This level of evidence – much like our Arm D non-interventional study (NIS) in HAVEN3, technically an observational study – can be considered a higher grade of evidence than effect estimates from parallel design non-randomized studies. As such we have included this data in a sensitivity analysis.

Supplementary Figure 2 illustrated the selection process that lead us from 94 identified in the SLR to five trials eligible for the NMA. Supplementary Table 8 lists each of these 94 studies and the reason for its inclusion or exclusion from the NMA.

### Supplementary Table 8. Study design characteristics and reason for inclusion/exclusion of studies in the NMA (hemophilia A - non-inhibitor population) (n=94).

| **ID** | **Study** | **Study type** | **Treatment** | **E/ P** | **N** | **Study duration** | **Study country** | **Primary publication** | **Linked publications** | **Inclusion for NMA, or reason for exclusion** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | LEOPOLD I  (NCT01029340) | RCT | BAY 81-8973 based on CS/EP then CS/ADJ vs.  BAY 81-8973 based on CS/ADJ then CS/EP | P  P | 30  32 | 12 months (optional extension: 12 months) | North America, Europe, Israel, South Africa and Asia | [20] | [21]; [22]; [23] | prophylaxis vs prophylaxis |
| 2 | LEOPOLD 2 (NCT01233258) | RCT | BAY 81-8973, low-dose vs.  BAY 81-8973 high-dose vs.  BAY 81-8973 | P  P  E | 28  31  21 | 12 months | Europe, South Africa, North America, South America, and Asia | [12] | [23]; [24] | INCLUDED |
| 3 | LEOPOLD KIDS (NCT01311648) | Single arm | BAY 81-8973 | P | 51 | 6-8 months | Bulgaria, Canada, Denmark, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Poland, Romania, US | [25] | [26] | <12 years; single arm |
| 4 | A-LONG (NCT01181128) | Parallel assignment (Partially randomized) | rFVIIIFc (Individualized prophylaxis) vs.  rFVIIIFc (Weekly prophylaxis) vs.  rFVIIIFc (Episodic treatment) | P  P  E | 118  24  23 | 32.1 weeks (median)  28 weeks (median)  28.9 weeks (median) | Europe, North America and others (Australia, New Zealand, Brazil, Hong Kong, India, Japan, Russia, and South Africa) | [27] | [28]; [29]; [30]; [31]; [32] | INCLUDED |
| 5 | Kids A-LONG (NCT01458106) | Single arm | rFVIIIFc | P | 71 | 26.3 weeks | NR | [33] | [34]; [35]; [36]; [37]; [31]; [32] | <12 years; single arm |
| 6 | ASPIRE (NCT01454739)  (extension to A-LONG) | Parallel assignment | rFVIIIFc (Individualized prophylaxis) vs.  rFVIIIFc (Weekly prophylaxis) vs.  rFVIIIFc (Modified prophylaxis) vs.  rFVIIIFc (Episodic treatment) | P  P  P  E | 109  27  17  14 | 80.9 weeks | NR | [38] | [39]; [40]; [41]; [42]; [43]; [44]; [45]; [46]; [47]; [48]; [49]; [50]; [51]; [52]; [53] | non-randomized study |
| 7 | Guardian 1  (NCT00840086) | Single arm | Turoctocog alfa | P | 150 | 29 months (long term follow-up: 29 months) | Brazil, Croatia, Germany, Israel, Italy, Japan, Malaysia, the Russian Federation, Serbia, Spain, Switzerland, Taiwan, Turkey, UK, US | [54] | [55]; [56] | single arm |
| 8 | Guardian 2 (NCT00984126) | Single arm | Turoctocog alfa (NovoEight) | P & E | 199 | NR | Brazil, Croatia, Germany, Israel, Italy, Japan, Latvia, Lithuania, Macedonia, Malaysia, Poland, Russian Federation, Republic of Serbia, Spain, Switzerland, Taiwan, Turkey, UK, US | [57]; [58] | [59]; [60]; [61]; [62]; [63]; [64]; [65] | single-arm study, without paired comparison of OD and prophylaxis |
| 9 | Guardian 3 (NCT01138501) | Single arm | Turoctocog alfa | P & E | 63 | 4.5 months (long term follow-up: 4.5 months) | Brazil, Italy, Lithuania, Macedonia, Malaysia, Poland, the Russian Federation, Serbia, Taiwan, Turkey, US | [66] | [56] | <12 years; single arm |
| 10 | Glamocanin 2015 | Single arm | rFVIII (turoctocog alfa) | P | 5 | NR | NR | [67] | - | <12 years; single arm |
| 11 | Pathfinder 2 (NCT01480180) | Single arm | Turoctocog alfa pegol (N8-GP); glycoPEGylaged recombinant factor VIII | P & E | 186 | ≥ 50 ED | Croatia, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, UK, Australia, Brazil, Israel, Japan, Republic of Korea, Malaysia, Taiwan, Turkey and country/countries from North America | [68] | - | single arm study, without paired comparison of OD and prophylaxis |
| 12 | Pathfinder 5 | Single arm | N8 GP - (turoctocog alfa pegol) | P & E | 68 | 26 weeks | NR | [69] | - | <12 years; single arm |
| 13 | SPINART (NCT00623480) | RCT | rFVIII-FS  rFVIII-FS | E  P | 42  42 | 1 year | US, Bulgaria, Romania, Argentina | [8,70] | [71]; [72]; [73]; [74] | INCLUDED |
| 14 | Kreuz 2005 | Single arm | rFVIII-FS (Kongenate FS, Bayer) | P & E | 61 | 3.5 years | Europe, Israel, North America | [75] | - | <12 years; single arm |
| 15 | Shi 2007 | Single arm | rFVIII-FS (Kogenate FS) | P | 49 | NR | China | [76] | - | <12 years; single arm |
| 16 | Vdovin 2011 | Parallel assignment | Kogenate (rFVIII-FS) – Regimen 1  Kogenate (rFVIII-FS) – Regimen 2  Kogenate (rFVIII-FS) – Regimen 3 | P  P  P | 11  13  8 | 9 months | Russia | [77] | - | prophylaxis vs prophylaxis |
| 17 | Collins 2010 | Single arm | rFVIII-FS (Kogenate FS/KOGENATE Bayer) | P & E | 20 | 13 months | US and Europe | [78] | - | single arm |
| 18 | LIPLONG | Single arm | rFVIII-FS | P | 72 | 52 weeks | Austria, Belgium, Canada, Croatia, Denmark, France, Germany, Israel, Italy, Norway, Poland, Spain, Netherlands, Turkey, UK, US | [79] | [80] | single arm |
| 19 | Yoshioka 2001 | Single arm | rFVIII-FS (Bayer) | E | 20 | 41.6 weeks | NR | [81] | - | single arm |
| 20 | Abshire 2000 | Single arm | rFVIII-FS | P & E | 71 | 24 weeks (Long term follow-up: 24 months (EU), 18 months (NA)) | US and North America | [82] | - | single arm |
| 21 | Giangrande 2002 | Single arm | Kogenate - factor VIII | P & E | 31 | At least 2 years and at least 20 EDs | 7 European countries and Israel | [83] | - | <12 years; single arm |
| 22 | Manco-Johnson 2007 | RCT | Recombinant factor VIII (Kogenate or Kogenate FS, Bayer HealthCare))  Recombinant factor VIII (Kogenate or Kogenate FS, Bayer HealthCare)) | P  E | 32  33 | Mean period of participation: 49 months | NR | [84] | - | <12 years |
| 23 | Zhao 2015 | Single arm | rfVIII-FS (Bayer’s sucrose formulated recombinant factor VIII) | P & E | 30 | 12 weeks on- demand then 12 weeks prophylaxis | China | [85] | - | single arm |
| 34 | Shirahata 2000 | Single arm | BAY 14-2222; Kogenate-FS | P | 5 | 4 weeks | Japan | [86] | - | single arm |
| 24 | Lusher 2004 | Single arm | rFVIII (Kogenate, Bayer) | P & E | 102 | 4.2 years | Europe, North America | [87] | - | single arm |
| 25 | Lusher 1993 | Single arm | rFVIII (Kogenate, Bayer) | P & E | 95 | 1.5 years | NR | [88] | - | <12 years; single arm |
| 26 | ESPRIT | RCT | rFVIII  rFVIII | P  E | 21  19 | 10 years | Italy | [89] | - | <12 years |
| 27 | Arkin 1991 | Single arm | rFVIII | E | 41 | NR | NR | [90] | - | single arm |
| 28 | White 1997 | Single arm | rFVIII (Recombinate) | P & E | 69 | 3.5 years | NR | [91] | - | single arm |
| 29 | Karimi 2015 | Single arm | rFVIII (Kogenate, Bayer) | P | 16 | NR | Iran | [92] | - | <12 years; single arm |
| 39 | Bray 1994 | Single arm | r-FVIII | E | 79 | 35 months | US | [93] | - | <12 years; single arm |
| 69 | Auerswald 2012 | Single arm | Advate rAHF-PFM | P & E | 55 | 3 years | NR | [94] | - | <12 years; single arm |
| 70 | Tarantino 2004 | Single arm | rAHF-PFM (Recombinate) | P | 107 | 75 days | Austria | [95] | - | single arm |
| 71 | Valentino 2012 | Single arm | ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method | P & E | 66 | 12 months prophylaxis and 6 months on-demand | US, Europe | [19] | - | INCLUDED in sensitivity analysis; single arm with paired comparative (prophylaxis vs OD) data |
| 83 | Aygören-Pürsün 1997 | Single arm | rFVIII (Kogenate, Bayer) | P & E | 39 | 1 year | Germany | [96] | - | single arm |
| 30 | Lindvall 2012 | Randomized, crossover | FVIII or FIX (standard prophylactic dosing)  or  FVIII or FIX (daily dosing) | P | 13 | 24 months (2 x 12 months) | Sweden | [97] | - | prophylaxis vs prophylaxis |
| 111 | Petrini 2001 | Single arm | FVIII; IX | P | 46 | 1 year | Sweden | [98] |  | <12 years |
| 32 | Gulshan 2016 | Single arm | Clotting Factor Concentrate (CFC) | P | 20 | 3 months | India | [99] | - | single arm |
| 31 | Verma 2016 | Parallelgroup, randomized | Factor VIII  Factor VIII | P  E | 11  10 | 11.5 months | India | [100] | - | <12 years |
| 40 | Crivianu-Gaita 2016 | Single arm | FVIII | P | 14 | 8 months | Canada | [101] | - | single arm |
| 33 | Powell 2000 | Single arm | Koate-DVI | P & E | 36 | 6 months | US | [102] | - | single arm |
| 35 | Lopez 2015 | Single arm | Moroctocog alfa (AF-CC) | NR | 208 | NR | Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Romania, Spain, Sweden, UK | [103] | - | single arm |
| 37 | Shiller 2015 | Single arm | Moroctocog alfa (Octofactor) | P | 12 | 21±1 weeks | NR | [104] | - | single arm |
| 41 | NCT00868530 | Single arm | Xyntha | E | 53 | 6 months | China | [105] | - | single arm |
| 62 | Courter 2001 | Single arm | B-domain deleted recombinant factor VIII (BDDrFVIII) | P & E | 101 | 5 years (long term follow-up: 5 years) | NR | [106] | - | single arm |
| 63 | Courter 2001 | Single arm | B-domain deleted recombinant factor VIII (BDDrFVIII) | P & E | 113 | 12 months (long term follow-up: 12 months) | Europe and US | [107] | - | <12 years; single arm |
| 48 | Klamroth 2015 | Single arm | Human-Cl rFVIII | P | 66 | NR | Europe | [108] | [109]; [110] | single arm |
| 49 | GENA-03 | Single arm | Nuwiq® (human-cl rhFVIII) | P | 59 | ≥6 months | NR | [111] | - | single arm |
| 50 | Successor study of GENA-03 | Single arm | Human-cl rhFVIII (Nuwiq) | P | 49 | NR | Europe | [112]; [113] | - | single arm |
| 51 | GENA-08 (NCT01125813) | Single arm | Nuwiq (human-cl rhFVIII) | P | 32 | 6 months | Austria, Bulgaria, Germany and the United Kingdom | [114]; [115] | - | single arm |
| 52 | GENA-01 (NCT00989196) | Single arm | Nuwiq (Human-cl rhFVIII) | E | 22 | ≥6 months | US, Germany and Bulgaria | [115] | - | single arm |
| 53 | Nemes 2008/ Nemes 2007 | Single arm | FVIII/VWF (IMMUNATE Solvent/Detergent) | P & E | 56 |  | Germany, Czech Republic, Austria, Hungary, Bulgaria, Poland | [116]; [117] | - | single arm |
| 55 | SWIFTLY-HA study | Parallel assignment | Voncento  Voncento | P  E | 18  17 | 12 months | NR | [118] | - | <12 years |
| 56 | SWIFT-HA study | Single arm | Plasma-derived VWF/FVIII concentrate (VONCENTO®) | P & E | 81 | 6 months | Bulgaria, Macedonia, Poland, Russian Federation | [119] | - | single arm study, without paired comparison of OD and prophy |
| 57 | SIPPET (NCT01064284) | RCT | Plasma-derived factor VIII containing von Willebrand factor  recombinant factor VIII | P & E  P & E | 125  126 | NR | NR | [120] | - | <12 years |
| 58 | Dmoszynska 2011 | Single arm | FVIII and VWF concentrate (Optivate) | P & E | 70 | 2 years (long term follow-up: 2 years) | Poland, UK | [121] | - | single arm |
| 59 | Matysiak 2011 | Single arm | Optivate (FVIII/VWF) | P & E | 30 | 26 weeks (long term follow-up: 26 weeks) | UK | [122] | - | <12 years |
| 60 | PROLONG-ATE | Single arm | BAX 855; pegylated full-length recombinant FVIII (rFVIII) | P & E | 137 | 6 months ± 2 weeks | US, Australia, Austria, Bulgaria, Czech Republic, Germany, Israel, Japan, Korea, Republic of, Lithuania, Malaysia, Netherlands, Poland, Romania, Spain, Sweden, Switzerland, Taiwan, Ukraine, UK | [123] | - | single arm study, without paired comparison of OD and prophy |
| 61 | Mullins 2016 | Single arm | Polyethylene glycol (peg)-ylated FVIII (BAX 855) | P | 66 | 6 months | NR | [124] | - | <12 years; single arm |
| 65 | NCT01568580 | Single arm | Beroctocog alfa | E | 70 | 21 months | Korea | [125] | - | single arm |
| 66 | Ledger 2016 | Single arm | rVIII-SingleChain | P | 81 | NR | NR | [126] | - | <12 years; single arm |
| 67 | AFFINITY  (NCT01486927) | Parallel assignment | rVIII-SingleChain | P  E | 146  27 | NR | NR | [127] | - | non-randomized study |
| 68 | Philipp 2001 | Single arm | Monoclate-P | E | 30 | 6 months (long term follow-up: 24 months) | US, Europe | [128] | - | single arm |
| 72 | Wolf 2004 | Single Arm (Study A)  Single Arm (Study B) | Factor VIII concentrate Haemoctin SDH  Factor VIII concentrate Haemoctin SDH | P & E  P & E | 13 (A)  41 (B) | 9 months  ≥6 months | Poland  Poland | [129] | - | single arm |
| 73 | Vossebeld 2003 | Single arm | AAFACT | P & E | 70 | 4 years | Netherlands | [130] | - | single arm |
| 91 | BB-2155-03/03LT  Lusher 1990 | Single arm | Monoclate | E | 38 | 6 months (long term follow-up: 24 months) | UK, USA, Netherlands, Israel | [131] |  | single arm |
| 74 | PROTECT VIII | Single arm (of parallel assignment) | BAY 94-9027 | P | 112 | 36 weeks | NR | [1] | - | single arm study, without paired comparison of OD and prophylaxis |
| 75 | PROTECT VIII Kids | Single arm | BAY94-9027 | P | 60 | ≥50 days | NR | [132] | - | <12 years; single arm |
| 76 | NCT01775618 | Single arm | BAY 94-9027 | P | 61 | 6 months | NR | [133] | - | <12 years; single arm |
| 87 | Leissinger 2001 | Single arm | High-dose DDAVP (desmopressin acetate) intranasal spray (Stimate®;1.5 mg/mL) | P & E | 124 | Mean duration of participation: 8 months | NR | [134] | - | single arm |
| 92 | 2014082018870N1  Eshgi 2015 | RCT | plasma-derived FVIII  vs.  Safacto (rFVIII) | E  E | 10  10 | 24 hours | Iran | [135] | - | OD vs OD |
| 38 | Smith 2005\* | PMS | rFVIII (REFACTO) | P & E | 60 | 6 months | Europe, New Zealand | [136] | - | single arm |
| 54 | Nemes 2012\* | PMS | FVIII/VWF product (haemoctin SDH; Biotest) | P & E | 109 | 82.6 months/patient | Germany, Hungary | [137] | - | single arm |
| 78 | Hay 1996\* | PMS | Monoclate-P | P | 97 | 284 days | UK | [138] | - | single arm |
| 86 | Yoshioka 2003\* | PMS | rFVIII (Kogenate) | E | 43 | 51 months | Japan | [139] | - | single arm |
| 88 | Calvez 2014\* | Pharmacosurveillance | rFVIII  rFVIII  rFVIII  rFVIII | NR | 97  111  48  27 | 75 EDs  75 EDs  75 EDs  75 EDs | France | [140] |  | single arm |
| 113 | HAVEN 4 | Single arm | Emicizumab | P | 41 | 6 months | Australia, Belgium, Japan, Poland, Spain, United States | (Internal Roche data) | [141,142] | single arm |
| 114 | Guardian 4 | Single arm | Turoctocog alfa | P | 59 | 4.4 years | NR | [143] | - | <12 years |
| 115 | Zhao 2017 | Single arm | rFVIII-FS (Kogenate) | P & E | 30 | 24 weeks | China | [144] | - | children aged 2–16 years |
| 116 | NHLBI R34 | Pilot RCT | rFVIII | P | 4 | 12 months | US | [145] | - | prophylaxis vs prophylaxis |
| 117 | Karimi 2018 | Single arm | rFVIII (Kogenate) or pdFVIII (Emoclot) | P | 33 | 12 months | Iran | [146] | - | <12 years; single arm |
| 118 | Chozie 2018 | RCT | KOATE-DVI (Antihemophilic Factor VIII) | P & E | 50 | 12 months | Indonesia | [147] | - | children with mean age 11 years |
| 119 | NuPreviq | Single arm | Human-cl rhFVIII (Nuwiq) | P | 66 | 6 months | 8 countries (Austria, Bulgaria, Germany, Hungary, Poland, Romania, Slovakia, and the UK) | [148] | - | single arm |
| 120 | NuProtect study | Single arm | Human-cl rhFVIII (Nuwiq) | P | 66 | 5 years | Belarus, Canada, France, Georgia, Germany, India, Italy, Moldova, Republic of, Morocco, Poland, Portugal, Russian Federation, Slovenia, Spain, Ukraine, United Kingdom, United States | [149] | - | single arm |
| 121 | Klukowska 2018 | Single arm | Octanate | P | 51 | 5 years | NR | [150] | - | single arm |
| 122 | PTP study /PUP study | Single arm | Moroctocog alfa | P & E | 60 | 24 months | 11 European countries (Bulgaria, Finland, Georgia, Greece, Italy, Romania, Serbia, Spain, Sweden, Turkey, Ukraine) | [151] | - | <12 years, single arm |
| 123 | Stasyshyn 2017 | Non-RCT | rVIII-SingleChain | P & E | 84 | 12 months | 19 countries (Europe, the USA and the rest of the world) | [152] | - | <12 years |
| 124 | CHIPS | Single arm | NR | P | 30 | 10 months | China | [153], Wanru 2018 | - | <12 years, single arm |
| 125 | AHEAD study\* | Registry | Advate | P & E | 715 | 4 years | 21 countries: Australia, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, France, Greece, Hungary, Italy, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland and United Kingdom. | [154] | [155] | registry |
| 126 | ABDR\* | Registry | FVIII or FIX | P & E | 718 | 12 months | Australia | [156] | - | registry |
| 127 | Kappa registry\* | Registry | NR | P & E | 173 | NR | Denmark, Norway, Sweden | [157] | - | registry |
| 128 | USHTCN\* | Registry | NR | P & E | 6196 | 12 years | US | [158] | - | registry |
| 129 | FranceCoag PUP cohort\* | Registry | pdFVIII (Factane); rFVIII (Kogenate); rFVIII (Advate) | P & E | 395 | NR | France | [140] | - | <12 years; registry |
| 130 | Dube 2018\* | PMS | rFVIII (Xyntha); rVIII (Wilate, Humate-P, Advate, Xyntha) | P & E | 135 | 12 months | Canada | [159] | - | PMS |

\*Registry/Postmarketing Surveillance (PMS); E: episodic; P: prophylactic; N: number of patients  
Gray shading: 18 new studies picked up in the SLR update (May 2018). None were eligible for the NMA.

Pink shading: studies included in the NMA (base case or sensitivity analysis).

### Supplementary Table 9. SUCRA values for treatments in all NMAs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study treatment** | **SUCRA, %** | | | |
|  | **Base case** | **SA1** | **SA2** | **SA3** |
| Emicizumab Q2W | 86.4 | 91.5 | 87.2 | 85.6 |
| Emicizumab QW | 79.1 | 75.2 | 78.4 | 79.1 |
| FVIII prophylaxis | 34.5 | 33.3 | 34.3 | 35.3 |
| On-demand FVIII | 0.0 | 0.0 | 0.0 | 0.0 |

SUCRA values range from 0% (the treatment is certainly ranked last) to 100% (the treatment is certainly ranked first).

FVIII, factor VIII; NA, not applicable; NMA, network meta-analysis; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis; SUCRA, Surface Under the Cumulative Ranking Area.

### Supplementary Table 10. Cross-tabulation of rate ratios for total treated bleeds – base-case NMA.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study treatment** | **Rate ratio with 95% credible intervals (row versus column)** | | | |
| **On-demand FVIII** | **FVIII prophylaxis** | **Emicizumab QW** | **Emicizumab Q2W** |
| **On-demand FVIII** | NA | 10.01 (6.20, 16.31) | 28.30 (11.93, 68.31) | 31.85 (13.11, 81.01) |
| **FVIII prophylaxis** | 0.10 (0.06, 0.16) | NA | 2.80 (1.06, 7.64) | 3.19 (1.19, 9.21) |
| **Emicizumab QW** | 0.04 (0.01, 0.08) | 0.36 (0.13, 0.95) | NA | 1.13 (0.46, 2.84) |
| **Emicizumab Q2W** | 0.03 (0.01, 0.08) | 0.31 (0.11, 0.84) | 0.88 (0.35, 2.18) | NA |

FVIII, factor VIII; NA, not applicable; NMA, network meta-analysis; Q2W, once every 2 weeks; QW, once weekly.

### Supplementary Figure 3. Heterogeneity assessment via ordinary pairwise meta-analyses, for studies included in NMAs.

A: All base-case studies that evaluated FVIII prophylaxis



B: All studies in SA3 (allowing inclusion of non-randomized studies) that evaluated FVIII prophylaxis



τ2 is the estimated between-study variance. I2 is the proportion of observed variance that is true between-study variance rather than random error (τ2 divided by the sum of τ2 and random error) [160].

Rate ratios compare the rate of treated bleeds between FVIII prophylaxis and no prophylaxis.

I2 values may be interpreted as low heterogeneity (0%–25%), low to moderate heterogeneity (25%–50%), moderate to high heterogeneity (50%–75%) and high heterogeneity (75%–100%).

CI, confidence interval; IRR, incidence rate ratio; NMA, network meta-analysis; SA, sensitivity analysis.

### Supplementary Table 11. Cross-tabulation of rate ratios for total treated bleeds – SA1 network meta-analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study treatment** | **Rate ratio with 95% credible intervals (row versus column)** | | | |
| **On-demand FVIII** | **FVIII prophylaxis** | **Emicizumab QW** | **Emicizumab Q2W** |
| **On-demand FVIII** | NA | 12.73 (11.70, 13.80) | 27.70 (20.16, 38.80) | 32.32 (22.98, 46.43) |
| **FVIII prophylaxis** | 0.08 (0.07, 0.09) | NA | 2.18 (1.58, 3.11) | 2.54 (1.79, 3.66) |
| **Emicizumab QW** | 0.04 (0.03, 0.05) | 0.46 (0.32, 0.63) | NA | 1.17 (0.73, 1.84) |
| **Emicizumab Q2W** | 0.03 (0.02, 0.04) | 0.39 (0.27, 0.56) | 0.86 (0.54, 1.37) | NA |

FVIII, factor VIII; NA, not applicable; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

### Supplementary Table 12. Cross-tabulation of rate ratios for total treated bleeds – SA2 network meta-analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study treatment** | **Rate ratio with 95% credible intervals (row versus column)** | | | |
| **On-demand FVIII** | **FVIII prophylaxis** | **Emicizumab QW** | **Emicizumab Q2W** |
| **On-demand FVIII** | NA | 9.18 (4.91, 17.33) | 28.17 (11.18, 67.72) | 32.41 (13.51, 81.81) |
| **FVIII prophylaxis** | 0.11 (0.06, 0.20) | NA | 3.04  (1.05, 9.24) | 3.52 (1.22, 10.93) |
| **Emicizumab QW** | 0.04 (0.01, 0.09) | 0.33 (0.11, 0.96) | NA | 1.17 (0.46, 3.07) |
| **Emicizumab Q2W** | 0.03 (0.01, 0.07) | 0.28 (0.09, 0.82) | 0.85 (0.33, 2.19) | NA |

FVIII, factor VIII; NA, not applicable; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

### Supplementary Table 13. Cross-tabulation of rate ratios for total treated bleeds – SA3 network meta-analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study treatment** | **Rate ratio with 95% credible intervals (row versus column)** | | | |
| **On-demand FVIII** | **FVIII prophylaxis** | **Emicizumab QW** | **Emicizumab Q2W** |
| **On-demand FVIII** | NA | 11.10 (7.30, 16.92) | 28.33 (11.16, 71.10) | 31.74 (12.67, 79.70) |
| **FVIII prophylaxis** | 0.09 (0.06, 0.14) | NA | 2.52 (0.91, 6.73) | 2.85 (1.04, 7.47) |
| **Emicizumab QW** | 0.04 (0.01, 0.09) | 0.40 (0.15, 1.10) | NA | 1.12 (0.47, 3.07) |
| **Emicizumab Q2W** | 0.03 (0.01, 0.08) | 0.35 (0.13, 0.96) | 0.89 (0.33, 2.15) | NA |

FVIII, factor VIII; NA, not applicable; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

### Supplementary Figure 4. Forest plot of rate ratios for total treated bleeds – SA1 network meta-analysis.



Plot shows ratios (with 95% credible intervals) for total treated bleeds (emicizumab versus all other comparators).

FVIII, factor VIII; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

### Supplementary Figure 5. Forest plot of rate ratios for total treated bleeds – SA2 network meta-analysis.



Plot shows ratios (with 95% credible intervals) for total treated bleeds (emicizumab versus all other comparators).

FVIII, factor VIII; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

### Supplementary Figure 6. Forest plot of rate ratios for total treated bleeds – SA3 network meta-analysis.



Plot shows ratios (with 95% credible intervals) for total treated bleeds (emicizumab versus all other comparators).

FVIII, factor VIII; Q2W, once every 2 weeks; QW, once weekly; SA, sensitivity analysis.

## Results: Subgroup analysis of the intra-patient comparison of the HAVEN 3 trial

### Supplementary Figure 7. Flow diagrams showing inclusion of patients in HAVEN 3 subgroup analysis.

A: WFH guidelines-based group



B: European label group



FVIII, factor VIII; NIS, non-interventional study; WFH, World Federation of Hemophilia.

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