**Supplementary material**

**Supplementary Table 1. Summary of studies assessing prophylaxis in hemophilia B**

| **Author, year** | **Study population** | **Efficacy outcomes of prophylaxis** |
| --- | --- | --- |
| **Retrospective observational studies** |
| Pettersson et al. 1981 [[1](#_ENREF_1)] | Severe hemophilia patients in Sweden; HA n=44, HB n=6 | Joint scores were assessed for up to 18 years. Patients on prophylaxis (25−30 IU/kg FIX at 4­−7 day intervals) rarely had joint deterioration compared with patients receiving on-demand treatment, almost all of which showed joint deterioration. |
| Nilsson et al. 1992 [[2](#_ENREF_2)] | Severe hemophilia patients in Sweden; HA n=52, HB=8 | Twice-weekly prophylaxis with 25–40 IU/kg FIX for 2–25 years, maintaining FIX levels above 1%, prevented arthropathy. Joint scores were lower versus a control group who received on-demand treatment. |
| Lofqvist et al. 1997 [[3](#_ENREF_3)] | Severe hemophilia patients in Sweden; HA n=29, HB n=5 | Joint scores remained unchanged over a 5-year period, suggesting prophylaxis (25–40 IU/kg twice-weekly in HB) can prevent joint damage. |
| Astermark et al. 1999 [[4](#_ENREF_4)] | Severe hemophilia patients in Sweden; HA n=108, HB n=13 | Initiating prophylaxis at a younger age was associated with less arthropathy and a shorter dosing interval was associated with fewer joint bleeds. |
| van der Berg et al. 2001 [[5](#_ENREF_5)] | Severe hemophilia patients in the Netherlands; HA n=70, HB n=5 | Over a mean follow-up of 15.6 years, tailored prophylaxis prevented arthropathy to a large extent. |
| Fischer et al. 2002 [[6](#_ENREF_6)] | Severe hemophilia patients in the Netherlands and France; HA n=131, HB n=24 | Patients on prophylaxis (for a median duration of 12.7 years) had fewer joint bleeds, lower joint scores and higher QoL compared with patients treated on demand. |
| **Prospective studies** |
| Morfini et al. 1976 [[7](#_ENREF_7)] | Severe HB patients (age 5–45 years), n=10 | Patients experienced significantly fewer joint bleeds with 7.5 IU/kg twice-weekly versus 15 IU/kg weekly FIX, rate difference -3.30 (95% CI: -5.50 to -1.10) bleeds/year. |
| Roth et al. 2001 [[8](#_ENREF_8)] | Moderate or severe HB, international study n=56 | Two-year trial with on-demand and prophylaxis arms (investigator selected). No direct comparison of on-demand and prophylaxis arms but prophylaxis was rated as ‘excellent’ or ‘effective in 93% of cases’.  |
| Monahan et al. 2010 [[9](#_ENREF_9)] | Severe HB patients (<6 years), n=25 | In pediatric patients receiving prophylaxis with rFIX (nonacog alfa) for a median duration of 31 weeks, 32% experienced no bleeding episodes and 91% had ≤1 joint hemorrhage during the study. |
| Shapiro et al. 2005 [[10](#_ENREF_10)] | Severe/moderate HB PUPs, international study, n=63 | Effective hemostasis was achieved in the 32 PUPs who received rFIX for routine prophylaxis, with 91% of prophylaxis responses rated "excellent." No direct comparison with on-demand treatment. |
| **Randomized cross-over studies** |
| Lindvall et al. 2012 [[11](#_ENREF_11)] | HA: n=8, HB: n=2 | The number of bleeding episodes with daily dosing (12 months) versus previous dosing regimen (12 month) was compared. A higher number of spontaneous bleeds occurred during daily versus previous prophylaxis in some patients. A 30% reduction in cost of factor was achieved with daily dosing but QoL decreased. |
| Valentino et al. 2014 [[12](#_ENREF_12)] | Severe/moderate HB in US, Canada and Europe, n=50 | Bleeding episodes with two prophylaxis regimens (once-weekly 100 IU/kg or twice-weekly 100 IU/kg) versus on-demand treatment periods with rFIX. Both prophylaxis regimens significantly (p<0.0001) reduced ABR versus on-demand treatment, with no significant difference in ABR between the two prophylaxis regimens (p=0.22). |
| **Prospective trials** |
| Windyga et al. 2014 [[13](#_ENREF_13)] | Severe/moderate HB, n=73, international cohort, mostly European. | Bleeding episodes with twice-weekly prophylaxis versus on-demand with rFIX (RIXUBIS®) for 3 months. The ABR for the prophylaxis group was 4.20 and was significantly (79%) lower than the ABR of a historical control group treated on-demand treatment (20.0).  |
| Martinowitz et al. 2015 [[14](#_ENREF_14)] | Severe/moderate HB patients in Israel and Bulgaria, HB n=17 | Weekly prophylaxis with rIX-FP (n=13) versus on-demand treatment (n=4) with rIX-FP. ABR was lower with prophylaxis versus on-demand treatment and prophylaxis reduced the AsBR by >85% compared with on-demand treatment. |
| **Non-randomized, open-label** |
| Powell et al. 2013 [[15](#_ENREF_15)] | Severe HB, previously treated, international trial; n=119 | Safety and efficacy trial with rFIXFc: weekly prophylaxis with 50 IU/kg; interval-adjusted prophylaxis (100 IU/kg every 10 days to start) and on-demand treatment were compared. ABR was lower with prophylaxis (3.0 [50 IU/kg weekly] and 1.4 [interval-adjusted]) versus on-demand treatment (17.7). |
| Collins et al. 2018 [[16](#_ENREF_16)]  | Severe or moderately severe HB, previously treated; n=76 | Patients treated with trenonacog alfa twice weekly had a lower median ABR (1.5) than subjects treated on demand (median ABR=16.1) |
| **Randomized trials** |  |  |
| Collins et al. 2014 [[17](#_ENREF_17)] | Severe/moderate HB, international study, n=74 | Patients/investigators selected prophylaxis (and then were randomized and blinded to one of two once-weekly dosing regimens: 10 or 40 IU/kg) or on-demand treatment with long-acting glycoPEGylated rFIX (N9-GP). Median ABR was lower with prophylaxis (1.0 with 40 IU/kg and 2.9 with 10 IU/kg) versus on-demand treatment (15.58). |
| **Open-label cross-over trials** |
| Kavakli et al. 2016 [[18](#_ENREF_18)] | Severe/moderate HB patients in Canada, Europe, Asia and Mexico, HB n=25 | Patients treated with rFIX (nonacog alfa) for 26 weeks followed by weekly prophylaxis with 100 IU/kg for 52 weeks. Median ABR was lower during prophylaxis (1.0) versus on-demand treatment (22.4). |
| Santagostino et al. 2016 [[19](#_ENREF_19)] | Severe or moderately severe HB, previously treated, international trial; n=63 | A total of 40 patients received routine prophylaxis (once every 7 days for six months, followed by either 7-, 10- or 14-day regimen for 6 months) and 23 patients received on-demand treatment with rIX-FP for six months followed by prophylaxis every 7-days for six months. The median ABR and AsBR were reduced by 91% and 100%, respectively, when patients switched from on-demand to 7-day prophylaxis.  |

ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; HA, hemophilia A; HB, hemophilia B, PUP, previously untreated patient; QoL, quality of life; rFIX, recombinant factor IX

**References**

1. Pettersson H, Nilsson IM, Hedner U et al. Radiologic evaluation of prophylaxis in severe haemophilia. Acta Paediatr Scand. 1981;70:565-570.

2. Nilsson IM, Berntorp E, Lofqvist T et al. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992;232:25-32.

3. Lofqvist T, Nilsson IM, Berntorp E et al. Haemophilia prophylaxis in young patients--a long-term follow-up. J Intern Med. 1997;241:395-400.

4. Astermark J, Petrini P, Tengborn L et al. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. Br J Haematol. 1999;105:1109-1113.

5. van den Berg HM, Fischer K, Mauser-Bunschoten EP et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. Br J Haematol. 2001;112:561-565.

6. Fischer K, van der Bom JG, Molho P et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. Haemophilia. 2002;8:745-752.

7. Morfini M, Mannucci PM, Mariani G et al. Evaluation of prophylactic replacement therapy in haemophilia B. Scand J Haematol. 1976;16:41-47.

8. Roth DA, Kessler CM, Pasi KJ et al. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. Blood. 2001;98:3600-3606.

9. Monahan PE, Liesner R, Sullivan ST et al. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. Haemophilia. 2010;16:460-468.

10. Shapiro AD, Di Paola J, Cohen A et al. The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B. Blood. 2005;105:518-525.

11. Lindvall K, Astermark J, Bjorkman S et al. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. Haemophilia. 2012;18:855-859.

12. Valentino LA, Rusen L, Elezovic I et al. Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects. Haemophilia. 2014;20:398-406.

13. Windyga J, Lissitchkov T, Stasyshyn O et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014;20:15-24.

14. Martinowitz U, Lissitchkov T, Lubetsky A et al. Results of a phase I/II open-label, safety and efficacy trial of coagulation factor IX (recombinant), albumin fusion protein in haemophilia B patients. Haemophilia. 2015;21:784-790.

15. Powell JS, Pasi KJ, Ragni MV et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369:2313-2323.

16. Collins PW, Quon DVK, Makris M. Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B patients. 2018;24:104-112.

17. Collins PW, Young G, Knobe K et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. Blood. 2014;124:3880-3886.

18. Kavakli K, Smith L, Kuliczkowski K et al. Once-weekly prophylactic treatment vs. on-demand treatment with nonacog alfa in patients with moderately severe to severe haemophilia B. Haemophilia. 2016;22:381-388.

19. Santagostino E, Martinowitz U, Lissitchkov T et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. Blood. 2016;127:1761-1769.