Received: 2 May 2018 | Revised: 31 July 2018 | Accepted: 6 August 2018

DOI: 10.1111/hae.13608

WILEY Haemophilia

ORIGINAL ARTICLE

Once-weekly prophylaxis with 40 IU/kg nonacog beta pegol (N9-GP) achieves trough levels of >15% in patients with haemophilia B: Pooled data from the paradigm™ trials

Johannes Oldenburg[1] | Manuel Carcao[2] | Steven R. Lentz[3] | Johnny Mahlangu[4] | Maria Elisa Mancuso[5] | Tadashi Matsushita[6] | Claude Négrier[7] | Wan Hui Ong Clausen[8] | Silke Ehrenforth[8] | Guy Young[9]

[1]Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany

[2]Division of Haematology/Oncology, Department of Paediatrics and Research Institute, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[3]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, , Iowa

[4]Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, NHLS and University of the Witwatersrand, Johannesburg, South Africa

[5]Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan

[7]Haemophilia and Thrombosis Centre, Louis Pradel Hospital, University Claude Bernard, Lyon, France

[8]Novo Nordisk A/S, Søborg, Denmark

[9]Hemostasis and Thrombosis Center, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, California

Correspondence
Guy Young, Hemostasis and Thrombosis Center, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA.
Email: gyoung@chla.usc.edu

Funding information
The trials were sponsored by Novo Nordisk A/S.

Introduction: Prophylaxis with replacement factor IX (FIX) reduces bleeding frequency and improves quality of life in haemophilia B patients. With prophylaxis, the likelihood of bleeding is lowered with increasing trough levels. New products with extended half-life (EHL) can maintain high factor activity levels over prolonged periods, compared with standard FIX products.

Aim: To evaluate the safety, efficacy and pharmacokinetics of the new recombinant FIX EHL product, nonacog beta pegol (N9-GP), using pooled data, with a focus on—but not limited to—prophylaxis at 40 IU/kg.

Methods: N9-GP has been investigated in males with congenital haemophilia B and FIX activity ≤2% in the paradigm™ clinical trial programme. This analysis includes pooled data from five completed paradigm™ trials conducted in previously treated adults, adolescents and children, focusing on results of prophylaxis with 40 IU/kg once-weekly intravenous dosing.

Results: In total, 115 previously treated patients were exposed to N9-GP. Of 54 patients (47%) treated with N9-GP 40 IU/kg once-weekly prophylaxis, 72% experienced no spontaneous bleeds over 1 year. In all patients receiving 40 IU/kg once-weekly, median overall annualized bleeding rate (ABR) was 1.03 (interquartile range 0.00; 2.89); median spontaneous ABR was 0.00 (0.00; 0.80). No patients developed inhibitors. Estimated mean steady-state trough levels with N9-GP 40 IU/kg once-weekly were ≥15% overall; 27.3% in adolescents and adults.

Conclusion: N9-GP 40 IU/kg once-weekly was well tolerated and effective in preventing bleeding, maintaining mean FIX activity levels ≥15% across all age groups. N9-GP may provide a new treatment option for preventing bleeding in haemophilia B patients.

KEYWORDS
factor IX, haemophilia B, nonacog beta pegol, prophylaxis, target joint, trough level

1 | INTRODUCTION

Haemophilia B is an X-linked recessive congenital bleeding disorder caused by a deficiency of factor IX (FIX).[1] For patients with haemophilia B, prophylaxis with FIX replacement therapy can reduce bleeding frequency, prevent haemophilic arthropathy and improve quality of life (QoL).[2–4] However, despite prophylaxis, joint bleeds and damage can still occur[5–7] and prophylaxis regimens can be challenging;[8,9] for example, standard FIX products can have half-lives of 18-23 hours,[10] thus requiring frequent injections and good adherence for treatment success.

High mean trough factor VIII activity levels of >15% (0.15 IU/mL) during regular prophylaxis may offer effective protection from bleeds,[11] and the same may be true for FIX activity. New products with an extended half-life (EHL) can change the paradigm of care; their modified pharmacokinetic (PK) profiles offer the potential to maintain higher factor activity levels over a prolonged period, lowering treatment burden compared with standard-half-life products.[1,12–14] The reduced dosing frequency of EHL prophylaxis products can lower total factor consumption,[15,16] with the lower frequency of administration likely improving patient adherence, treatment outcomes and QoL.[3,12,13]

Nonacog beta pegol (N9-GP) is a recombinant FIX that has an EHL.[1] N9-GP has improved PK properties: higher recovery, greater area under the curve (AUC), and a fivefold increase in terminal half-life compared with standard FIX products.[1] These improvements offer the possibility of maintaining near-normal (nonhaemophilic) FIX activity levels (>40%; 0.40 IU/mL) with once-weekly prophylaxis.[17]

The safety, efficacy and PK of N9-GP in patients with haemophilia B have been investigated in the paradigm™ clinical trials.[1,2,18–20] This analysis presents pooled data from five completed paradigm™ trials conducted in previously treated patients with haemophilia B, with a focus on once-weekly prophylaxis with N9-GP 40 IU/kg, and including results for once-weekly prophylaxis with N9-GP 10 IU/kg and on-demand treatment with N9-GP 40 or 80 IU/kg. Results from the range of N9-GP regimens are analysed to ensure that the safety data are appropriately and comprehensively reported. The analysis is supplemented by previously published data from the paradigm trials. This study aims to provide new insights into the safety, efficacy and PK of N9-GP in a larger population of patients than is usual in individual trials, across distinct age groups.

2 | MATERIALS AND METHODS

Data from completed paradigm™ trials that evaluated the efficacy, safety or PK of N9-GP were included in these analyses (see Table S1 for an overview of these trials).

2.1 | Trial design

Details of the methods of individual paradigm™ trials included in the pooled analyses (paradigm™1, 2, 3, 4, 5) have been published previously.[1,2,18–20] The trials were all multicentre and multinational, including patients from 16 countries (Table S2). Randomization and blinding details are provided in the Appendix S1.

2.2 | Patients and treatment

All patients were previously treated males with moderately severe or severe congenital haemophilia B and FIX activity ≤2%. In all trials, N9-GP was administered intravenously (iv) as bolus injections.[1,2,18–20] Additional information on the N9-GP protein is provided in the Appendix S1.

2.2.1 | Prophylaxis

Prophylaxis treatment regimens for adolescents and adults in paradigm™2 and paradigm™4 included N9-GP 10 or 40 IU/kg once-weekly. In paradigm™5, paediatric patients received prophylaxis with N9-GP 40 IU/kg once-weekly.[2,18,20]

2.2.2 | Treatment of bleeds

Bleeds were classified as mild, moderate (ie uncomplicated joint bleeds, muscle bleeds without compartment syndrome, or mucosal or subcutaneous bleeds) or severe (ie all intracranial, retroperitoneal, iliopsoas and neck bleeds, muscle bleeds with compartment syndrome, and bleeds associated with a decrease in haemoglobin level >3 g/dL). All reported bleeds treated with N9-GP were included in the efficacy analyses.

2.2.3 | On-demand treatment

N9-GP on-demand treatment included treatment of bleeds only, as described above.

2.3 | Trial objectives

Primary and key secondary trial objectives are detailed in the Appendix S1.

2.4 | Analytical methods

2.4.1 | FIX inhibitors and FIX activity

Tests for FIX inhibitors (titres ≥0.6 Bethesda units) were conducted as previously described using the standard Bethesda assay and a modified heat/cold Nijmegen Bethesda assay.[2,20,21]

PK assessments of FIX activity were primarily based on an activated partial thromboplastin time (aPTT)-based one-stage clotting assay performed on a coagulation analyser (Siemens BCS® XP analyser [Dade Behring, Marburg, Germany]) using SynthAFax (Instrumentation Laboratories, Brussels, Belgium) as an aPTT reagent. The FIX activity in test samples was measured using a product-specific calibrator (N9-GP) at a central laboratory (Esoterix Inc,

Englewood, CO, USA). Efficacy of prophylaxis was also evaluated using FIX activity as a surrogate marker.

2.4.2 | Target joint International Society on Thrombosis and Haemostasis (ISTH) definition

A target joint is defined as ≥3 bleeds within 6 months. Where there have been ≤2 bleeds into a current target joint within 12 consecutive months, the joint is no longer considered a target joint.[22]

2.4.3 | Patient-reported outcomes

Patient-reported outcomes were collected from adult/adolescent patients using the EuroQoL-5 Dimensions (EQ-5D) visual analogue scale (VAS) and Haemophilia-Adults-Quality of Life (Haem-A-QoL). These questionnaires measured generic health outcome and disease-specific QoL, respectively. Age-specific Haemo-QoL questionnaires were used for paradigm™5.

2.5 | Statistical methods

No apparent differences between trials, treatment regimens or age groups were observed in the haemostatic response of N9-GP when used for treatment of bleeds. The same treatment for control of bleeds, 40 IU/kg for mild/moderate bleeds and 80 IU/kg for severe bleeds, was used across all trials. A pooled haemostatic response that included all bleeds from all treatment arms in all trials is therefore presented here. All other efficacy endpoints are presented either by treatment regimen or by age group. Safety data from all completed trials in previously treated patients (PTPs) were pooled (Appendix S1).

No formal hypothesis testing was performed on pooled efficacy data and the prevalence of the success outcomes was consistent across trials.

The extension phase of paradigm™5 was ongoing at the time of this pooled analysis. All data up to the last patient to complete the main phase of the trial were included in the analysis.

All statistical analyses were based on the full analysis set (FAS); that is, all patients exposed to N9-GP. All patients exposed to N9-GP in the completed trials were included in the safety analyses.

Further details on the statistical methods are provided in the Appendix S1.

3 | RESULTS

3.1 | Patients

The flow of patients in the paradigm™ clinical trial programme (pooled analysis) is shown in Figure 1. A total of 115 unique PTPs were exposed to N9-GP in the five completed clinical trials. The majority of patients participated in more than one trial; thus, the sum of patients in the individual trials is higher than the total number of

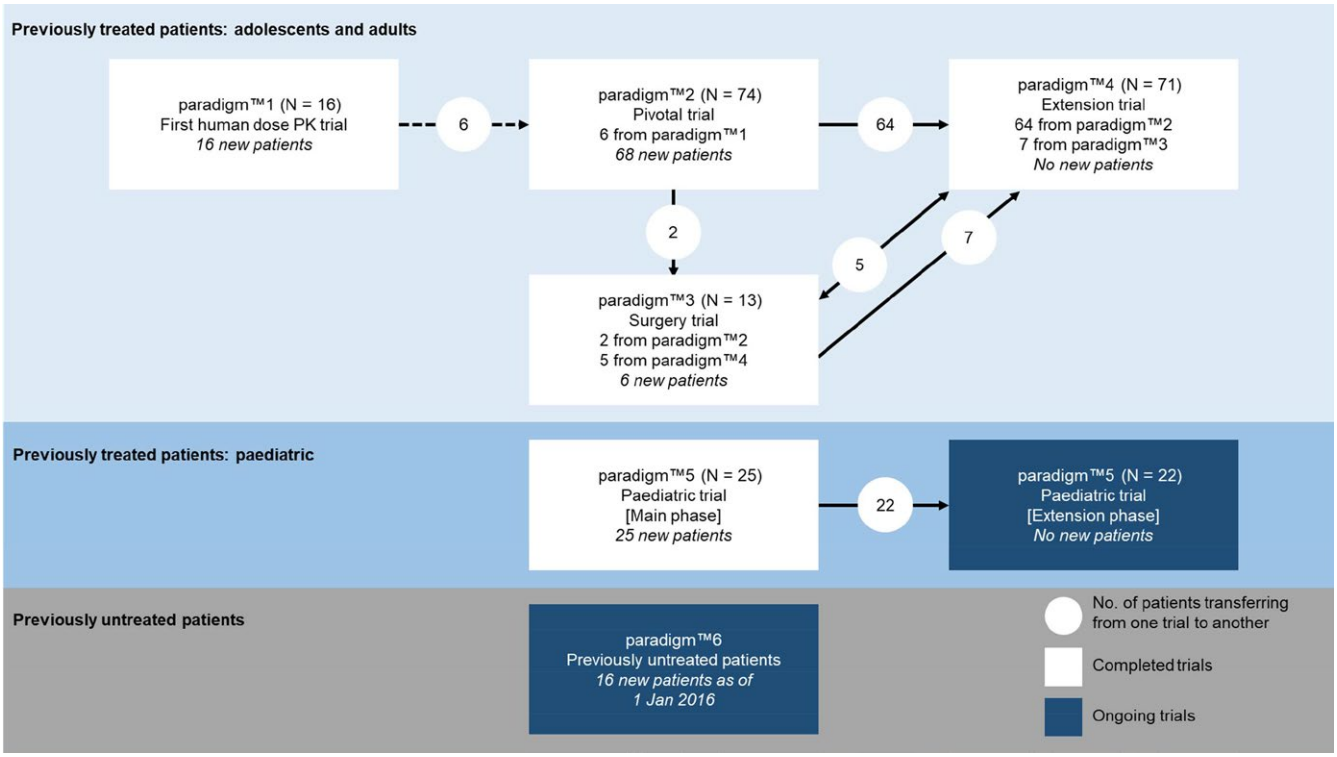


FIGURE 1 Flow of patients in the paradigm™ clinical trial programme (pooled analysis). The figure shows the flow of patients through the trials. In the completed trials (white boxes), a total of 115 unique previously treated patients were exposed to N9-GP. "New" patients (italics) refer to the number of patients exposed to N9-GP for the first time in each trial

unique patients. Of the 115 patients, 90 were adults or adolescents, 25 were children (Table 1). The majority were from the United States (n = 32), the United Kingdom (n = 16), Germany and Japan (n = 11 each). In total, 105 of 115 patients were included in the four trials that comprise the efficacy results (the remaining 10 patients participated in the single-dose PK trial only and are not included).

In the trials evaluating prophylactic efficacy, 30 patients received 10 IU/kg N9-GP once-weekly prophylaxis, 54 patients received 40 IU/kg once-weekly prophylaxis, and 15 patients were treated on-demand. The annualized bleeding rate (ABR) results include data from paradigm™2 and 5, and exclude data from paradigm™4 due to the bias that results from switching of treatment regimens (where patients could choose their own treatment) within the study.

Baseline demographics for all unique patients participating in the pooled analysis are shown in Table 1. Mean (standard deviation) patient age was 26.0 (15.8) years. At trial entry, 61.7% of patients were on prophylaxis and 38.3% were receiving on-demand treatment.

A total of 91.5% of adolescents/adults in paradigm™2 had problem joints at baseline, as had 16% of children in paradigm™5[18] (Table S3).

TABLE 1 Baseline demographics for all unique patients participating in the paradigm™ clinical trial programme (pooled analysis), presented by age group

	1–6 y	7–12 y	13–17 y	18–65 y	Total
No. of patients	12	13	18	72	115
Age at baseline in first trial (year)					
Mean (SD)	3.1 (1.7)	9.6 (1.6)	14.8 (1.4)	35.7 (11.6)	26.0 (15.8)
Race, n (%)					
White	8 (66.7)	5 (38.5)	15 (83.3)	47 (65.3)	75 (65.2)
Black	-	1 (7.7)	-	6 (8.3)	7 (6.1)
Asian	4 (33.3)	4 (30.8)	1 (5.6)	16 (22.2)	25 (21.7)
Other	-	3 (23.1)	2 (11.1)	3 (4.2)	8 (7.0)
Classification of haemophilia B, n (%)					
Moderate	-	-	4 (22.2)	10 (13.9)	14 (12.2)
Severe	12 (100.0)	13 (100.0)	14 (77.8)	62 (86.1)	101 (87.8)
Hepatitis C and HIV status,[a] n (%)					
Hepatitis C antibody					
Low positive	-	-	-	3 (4.2)	3 (2.6)
Positive	-	-	-	45 (62.5)	45 (39.1)
HIV–1/2 antibody positive	-	-	-	9 (12.7)	9 (8.0)
Current treatment prior to trial, n (%)					
On-demand	1 (8.3)	2 (15.4)	4 (22.2)	37 (51.4)	44 (38.3)
Prophylaxis	11 (91.7)	11 (84.6)	14 (77.8)	35 (48.6)	71 (61.7)
Previous prophylaxis patients					
Months on prophylaxis					
Mean (SD)	22.4 (18.5)	90.5 (31.6)	104.3 (49.9)	154.9 (161.6) 37.8	113.8 (124.2) 40.6
Prophylaxis dose level (U/kg)					
Mean (SD)	37.5 (11.5)	57.7 (33.6)	36.9 (15.2)	37.8 (15.5)	40.6 (19.9)
FIX level limit, n (%)	n = 10	n = 12			n = 22
<0.6%	2 (20.0)	-	-	-	2 (9.1)
<1.0%	8 (80.0)	12 (100.0)	-	-	20 (90.9)
FIX level at screening	n = 11	n = 13	n = 18	n = 55	n = 97
Mean (SD)	2.1 (0.7)	4.6 (1.7)	3.2 (1.8)	2.9 (1.9)	3.1 (1.9)

FIX, factor IX; PTP, previously treated patient; SD, standard deviation.

The pooled analysis involved 115 PTPs, age 1-65 y. The extension phase of paradigm™5 was ongoing at the time of this pooled analysis. All data up to the last patient to complete the main phase of the trial were included in the analysis. Patients in paradigm™4 have not been included as their baseline information is the same as in the first trial; that is, either paradigm™2 or 3. Only patients from paradigm™3 not previously treated in paradigm™2 are included. For patients who participated only in the paradigm™1 trial, history data are from this trial. For all other patients, history data are from the first phase 3 trial. Classification of haemophilia: moderate, 1-≤2% FIX activity; severe, <1% FIX activity.

[a]Taken at baseline in the first trial in which each patient participated and had a baseline assessment.

3.2 | Safety

In the completed trials, 115 PTPs were exposed to N9-GP for 8,801 exposure days, corresponding to approximately 170 patient-years (Table 2). No patients developed N9-GP inhibitors. Anti-N9-GP binding antibodies were identified in three patients. None of these antibodies had any inhibitory effect, and detection of antibodies did not correlate with any adverse events (AEs) or with reduced trough FIX activity levels.

A total of 647 AEs were reported in 98 (85.2%) patients; the overall rate was 3.8 AEs per patient-year of exposure (Table 2, Table S4). The most commonly reported AEs are detailed in Table S5. Overall, there were no unexpected safety signals, and no thromboembolic events were reported, nor systemic changes over time for haematological, hepatic or renal parameters.

3.2.1 | Pharmacokinetics

Single-dose administration

For all patients, FIX activity remained >0.05 IU/mL for up to 168 hours after single-dose administration of N9-GP 40 IU/kg.[17] Geometric mean FIX activity 168 hours postdosing for single dose 40 IU/kg was 0.08 IU/mL (1-6 years), 0.11 IU/mL (7-12 years), 0.15 IU/mL (13-17 years) and 0.17 IU/mL (≥18 years). FIX activity declined exponentially after dosing, and was generally lower in younger than in older patients.

Single-dose PK parameters for N9-GP 40 IU/kg in the completed trials are presented in Table 3. An increasing incremental recovery (0.015 [IU/mL]/[IU/kg] in age 1-6 years; 0.023 [IU/mL]/[IU/kg] in adults) and a decrease in clearance (0.8 and 0.4 mL/h/kg, respectively) with age was observed, and the half-life was higher in adolescents and adults (up to 89.4 hours) than in children (up to 76.3 hours).

TABLE 2 Overview of adverse events in the paradigm™ clinical trial programme (pooled analysis), presented by age group

	1–6 y n (%)	7–12 y n (%)	13–17 y n (%)	18–65 y n (%)	Total N (%)
No. of patients	12	13	18	72	115
Total time in trial (years)	12.6	16.5	35.7	105.0	169.9
Total no. of exposure days	682	906	1,914	5,299	8,801
All adverse events	12 (100.0)	12 (92.3)	17 (94.4)	57 (79.2)	98 (85.2)
Serious adverse events	-	1 (7.7)	2 (11.1)	8 (11.1)	11 (9.6)
Adverse events by severity					
Mild	12 (100.0)	12 (92.3)	16 (88.9)	53 (73.6)	93 (80.9)
Moderate	5 (41.7)	2 (15.4)	6 (33.3)	30 (41.7)	43 (37.4)
Severe	-	-	1 (5.6)	9 (12.5)	10 (8.7)
Adverse events by relationship[a]					
Probably or possibly related	1 (8.3)	3 (23.1)	2 (11.1)	17 (23.6)	23 (20.0)
Unlikely related	12 (100.0)	11 (84.6)	17 (94.4)	57 (79.2)	97 (84.3)
Adverse events leading to withdrawal	-	-	-	2 (2.8)	2 (1.7)

%, percentage of patients with adverse event; N/N, number of patients with adverse event; PTPs, previously treated patients.
The pooled analysis involved 115 PTPs age 1-65 y. The extension phase of paradigm™5 was ongoing at the time of this pooled analysis. All data up to the last patient to complete the main phase of the trial were included in the analysis. All adverse events listed were treatment-emergent. An exposure day is defined as a day when the patient received at least one dose of N9-GP. Age is defined for each patient as age at baseline in the first trial.
[a]The causality for one adverse event (overdose in paradigm™1) was captured in the safety database only and is therefore not included in this table, which is based on data in the clinical database. The event was judged to be unlikely related to N9-GP treatment by the investigator.

TABLE 3 Single-dose PK parameters of N9-GP 40 IU/kg in completed clinical trials (pooled analysis), presented by age group

PK parameter [geometric mean (CV)]	1–6 y (n = 12)	7–12 y (n = 13)	13–17 y (n = 3)	18–65 y (n = 6)
Half-life (h)	69.6 (15.8)	76.3 (25.5)	89.4 (24.1)	83.0 (22.5)
IR (IU/mL)/(IU/kg)	0.015 (7.3)	0.016 (16.2)	0.020 (14.7)	0.023 (11.3)
$AUC_{(0-inf)}$ (IU*h/mL)	46.2 (14.1)	56.2 (19.1)	79.9 (34.7)	90.6 (16.1)
CL (mL/h/kg)	0.8 (13.0)	0.6 (21.9)	0.5 (30.4)	0.4 (14.7)

$AUC_{(0-inf)}$, area under the curve from time 0 to infinity; CL, clearance; CV, coefficient of variation; h, hours; IR, incremental recovery; PK, pharmacokinetic.

Steady-state FIX levels

Steady-state trough levels were available for all patients and estimated mean data with 40 IU/kg N9-GP once-weekly were ≥15% (0.15 IU/mL) in all age groups. In adolescents and adults, mean steady-state trough levels were 27.3% (95% confidence interval [CI] 24.8; 30.0)—almost twice as high as those in children aged 1-6 years (15.4% [12.7; 18.6]). Trough levels were 19.0% (15.9; 22.8) in children aged 7-12 years. Corresponding peak levels were 92.6% (85.5; 100.0), 65.5% (60.6; 70.7) and 71.4% (66.3; 77.0).

When steady-state FIX activity profiles were predicted using a one-compartment distribution model, patients treated with N9-GP 40 IU/kg once-weekly were predicted to have FIX activity >40% for 5.4 days per week in adolescents and adults (Figure 2), and for 2.3 days per week in children.[17]

Cumulative time above 15% was predicted to be the entire weekly dosing interval in adolescents and adults (Figure 2), and 6.4 days per week in children.[17]

3.3 | Efficacy

3.3.1 | Treatment of bleeds

In total, 597 bleeds were treated in 79 (75%) of the 105 patients who were evaluated for efficacy.

Clinical efficacy of N9-GP for the control of bleeding episodes is shown in Figure 3. The overall success rate (defined as excellent or good using the four-point scale) for the treatment of bleeds in all trials was 93% (haemostatic response was missing for six bleeding episodes). The majority of bleeds (97%) were successfully treated with 1-2 injections of N9-GP (87% were treated with 1 dose, 10% with 2 doses, 3% with ≥3 doses). The total median dose level of N9-GP used for the treatment of all bleeds was 42.3 IU/kg (range, 20.3-444.7). This dose was similar between patients on prophylaxis (42.4 IU/kg) and those taking N9-GP on-demand (42.1 IU/kg).

The haemostatic response by prophylaxis dose was assessed in paradigm™2, where the success rate for patients on N9-GP 40 IU/kg was 97% and for those on 10 IU/kg was 87%.[2]

3.3.2 | Prophylaxis

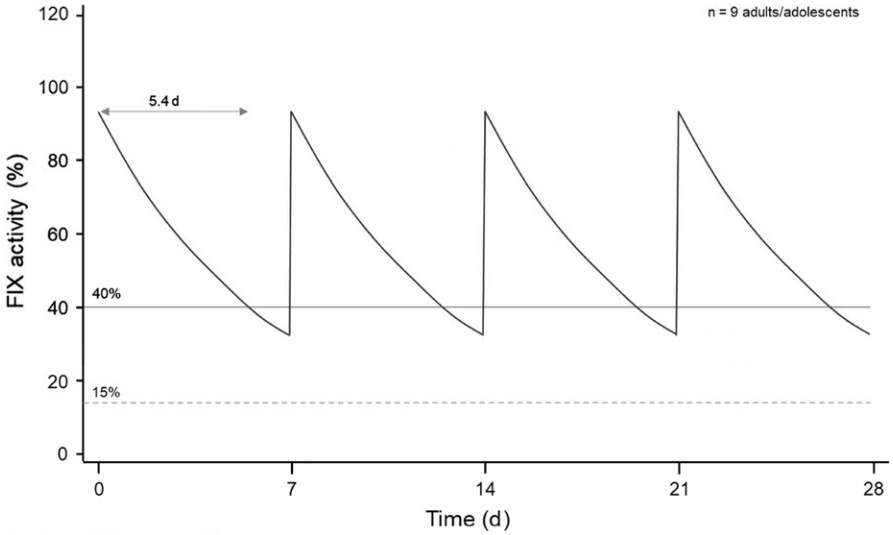
In the pooled analysis, 39 (72%) of the 54 patients treated with 40 IU/kg once-weekly prophylaxis experienced no spontaneous bleeds. Forty-six spontaneous bleeds occurred in 15 (28%) patients (range, 0-11 per patient) over a mean treatment period of 1.1 years; 33 spontaneous bleeds (72%) occurred in eight adults. Estimated spontaneous ABR (AsBR) for all age groups receiving 40 IU/kg was 0.71 (95% CI 0.32; 1.56); median AsBR was 0.00 (interquartile range [IQR] 0.00; 0.80). Overall median ABR increased slightly with age, while median ABRs for spontaneous, traumatic and joint bleeds were 0.00 among all patients (Table 4). Adult, adolescent and paediatric patients on prior prophylaxis treated with 40 IU/kg N9-GP once-weekly had a substantial reduction in estimated AsBR during the trial (Figure S1).

Twenty (69%) of the 29 adolescent and adult patients treated with 40 IU/kg once-weekly prophylaxis experienced no spontaneous bleeds. Overall estimated AsBR was 1.22 [95% CI 0.46; 3.25].

Of the 25 children (22% of the total) treated with 40 IU/kg once-weekly prophylaxis, 19 (76%) experienced no spontaneous bleeding episodes: 10/12 (83%) aged 1-6 years, and 9/13 (69%) aged 7-12 years. Thirteen spontaneous bleeds occurred in six (24%) patients (overall estimated AsBR 0.45 [95% CI 0.18; 1.08]).

3.3.3 | Target joints

A total of 20 target joints (modified International Society on Thrombosis and Haemostasis definition) in 13 patients were reported at baseline in paradigm™2 with 40 IU/kg once-weekly N9-GP prophylaxis. Each patient had ≥350 days in the trial. Of these, 18/20 (90%) target joints were resolved (≤2 bleeding episodes in the



d, days; FIX, factor IX.

FIGURE 2 Predicted FIX activity level at steady state in adults/adolescents with N9-GP 40 IU/kg once-weekly (paradigm™2). The grey solid line shows the lower limit of the nonhaemophilia range (>40%) according to the World Federation of Hemophilia guidelines[31]

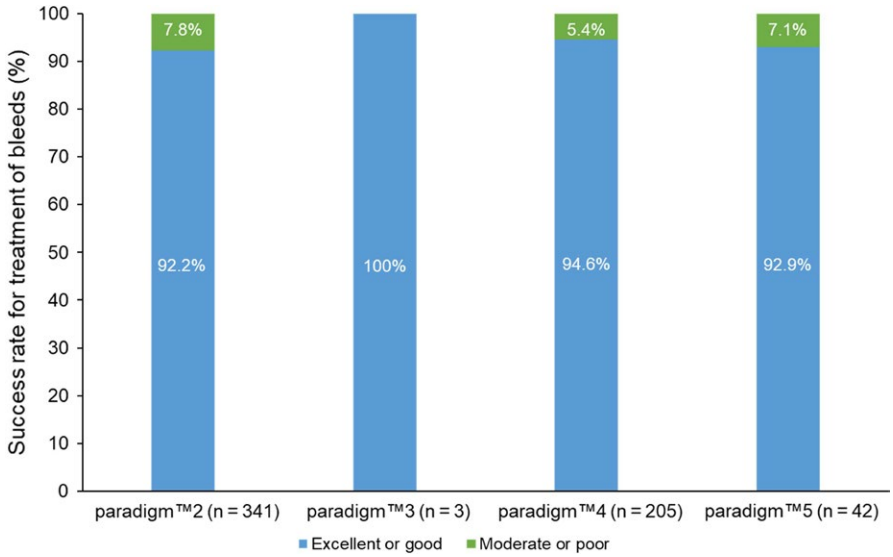


FIGURE 3 Clinical efficacy of N9-GP for the control of bleeding episodes in the paradigm™ clinical trial programme (pooled analysis)

TABLE 4 Annualized bleeding rate in completed clinical trials with N9-GP 40 IU/kg once-weekly (pooled analysis), presented by age group

Bleeding rate	<13 y (n = 25)	13–65 y (n = 29)	All patients, 1–65 years (N = 54)
$ABR_{spontaneous}$, median (IQR)	0.00 (0.00; 0.00)	0.00 (0.00; 0.99)	0.00 (0.00; 0.80)
$ABR_{traumatic}$, median (IQR)	0.68 (0.00; 1.93)	0.00 (0.00; 2.05)	0.00 (0.00; 1.96)
ABR_{joint}, median (IQR)	0.00 (0.00; 0.80)	0.97 (0.00; 2.07)	0.00 (0.00; 1.97)
Overall ABR, median (IQR)	1.00 (0.00; 2.06)	1.04 (0.00; 4.01)	1.03 (0.00; 2.89)
Patients with no bleeding episodes, n (%)	10 (40.0)	13 (44.8)	23 (42.6)
Patients with no spontaneous bleeding episodes, n (%)	19 (76.0)	20 (69.0)	39 (72.2)

ABR, annualized bleeding rate; IQR, interquartile range.

same joint) during the trial.[23] By the end of the extension trial (paradigm™4), resolution of target joints was 100% with N9-GP 40 IU/kg once-weekly.[23]

A total of 66.7% of patients in paradigm™2 with target joints at baseline on 40 IU/kg once-weekly prophylaxis reported no target joint bleeds during the trial, versus 7.7% of patients on 10 IU/kg prophylaxis.[2] No bleeds were reported in 56% of baseline target joints treated with 40 IU/kg once-weekly prophylaxis, versus 0% treated with 10 IU/kg.

In paradigm™2 patients who had target joints, 138 target joint bleeds were reported: 49 with 10 IU/kg and 19 with 40 IU/kg. The haemostatic success rate for treatment of these bleeds was 89.5%.

Estimated target joint ABR was 0.94 (95% CI 0.12; 7.67) bleeds/patient-year for the 17 patients on 40 IU/kg once-weekly prophylaxis in paradigm™2 and 5 (Table S6).

In paradigm™5, over 52 weeks, two paediatric patients had one target joint each (one in the left ankle, one in the right toe) at baseline. There were two target joint bleeds in two patients. Overall estimated target joint ABR was 0.07 (95% CI 0.02; 0.23). There was a 100% success rate in treating target joint bleeds. No spontaneous bleeds were reported in target joints.[18]

3.3.4 | Patient-reported outcomes

In adolescents and adults treated with N9-GP 40 IU/kg once-weekly, statistically significant improvements in QoL from baseline to end of trial were demonstrated in the EuroQoL-5 Dimensions visual analogue scale (EQ-5D VAS) [$P = 0.030$] and Haemophilia-Adults-Quality of Life (Haem-A-QoL) [$P = 0.017$] questionnaires (Figure 4). Mean change from baseline in EQ-5D VAS score was 8.2 (positive score indicates improvement); the mean change was higher in patients taking pretrial prophylaxis (9.0). Mean change from baseline in patients ≥17 years old in Haem-A-QoL score was −6.4 (negative score indicates improvement), which was driven by significant improvements in the key Haem-A-QoL domains of feeling, sport and partnership (all $P < 0.05$).[24] The improvement in Haem-A-QoL was significantly greater with N9-GP 40 IU/kg compared with 10 IU/kg once-weekly ($P = 0.049$),[24] but the difference between regimens for change in EQ-5D VAS was not significant ($P = 0.514$).

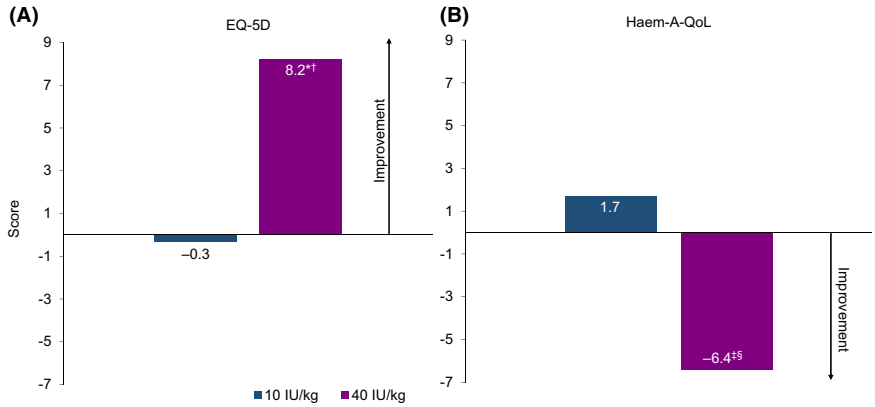


FIGURE 4 Health-related quality of life following N9-GP therapy—change from baseline to end of trial (paradigm™2) in a) EQ-5D and b) Haem-A-QoL, presented by dose. *P = 0.030 vs baseline; †P = 0.514 vs 10 IU/kg; ‡P = 0.017 vs baseline; §P = 0.049 vs 10 IU/kg. For EQ-5D VAS score, a positive change from baseline indicated an improvement. For Haem-A-QoL score, a negative change from baseline indicated an improvement. *P* values for change from baseline are from a nonparametric Wilcoxon signed rank test. *P* values for difference between doses are from a nonparametric Mann-Whitney test. The Haem-A-QoL score is applicable to patients of aged 17 years and above. EQ-5D, EuroQoL-5 Dimensions; Haem-A QoL, Haemophilia-Adults-Quality of Life; VAS, visual analogue scale

Data on paediatric QoL were inconclusive due to the use of different questionnaires in different age groups and the small sample size.

4 | DISCUSSION

The haemostatic efficacy of N9-GP was demonstrated by an overall success rate of 93% for treating bleeds, at doses of 20.3-444.7 IU/kg, with the majority (97%) resolved with 1-2 injections. Prophylactic efficacy of N9-GP 40 IU/kg once-weekly was confirmed. Low median overall and AsBRs across all age groups were similar to, or lower than, rates reported for similar doses of currently licensed rFIX EHL products.[14,25] The 40 IU/kg prophylactic dose was also more effective than the 10 IU/kg regimen. Median joint ABR following prophylaxis with N9-GP 40 IU/kg once-weekly was higher in adolescents and adults (0.97) than in paediatric patients (0.00); an expected result, given that joints in adult haemophilia patients are more likely to have underlying disease. Considering that joint disease is irreversible,[26] adults may, therefore, be at greater risk of experiencing bleeds.

Improvements to the management of haemophilia B include better protection from bleeding episodes.[12,18] PK analyses showed that once-weekly prophylaxis with N9-GP 40 IU/kg maintained mean FIX activity at ≥15% across all age groups.[17] A trough level >15% (0.15 IU/mL) has been suggested as a threshold for avoiding bleeding episodes.[11] Despite relatively high FIX trough levels, 28% of patients treated with 40 IU/kg once-weekly prophylaxis experienced spontaneous bleeds; 33 of 46 spontaneous bleeds were in adults. This may be due to existing and irreversible joint disease, particularly in adults (in patients aged 13-65 years in paradigm™2 treated with 40 IU/kg prophylaxis, 93.1% had problem joints at baseline). Furthermore, bleeding phenotype may not always correlate with factor activity.[26] Nonetheless, with its EHL of 93 hours and high incremental recovery of 2% providing the possibility of maintaining high FIX activity levels,[1] N9-GP may offer effective bleed protection, which lasts throughout the week in adolescents and adults.

Results from this analysis align with those of a previous analysis in this trial population, showing that patients had high FIX activity levels during the entire period between N9-GP dose administrations,[17] and align with those for currently licensed rFIX EHL prophylaxis regimens.[14] According to published PK results, patients >13 years and children <12 years old spent approximately 80% and 30% of the week, respectively, with FIX activity levels in the "non-haemophilia" range.[17] The trend of increasing incremental recovery and lower clearance (mL/h/kg) of N9-GP across the age groups has previously been described for other FIX products, and corresponds to a higher volume of distribution per kg body weight in younger compared with older subjects.[27]

This observed high bleed protection with N9-GP 40 IU/kg once-weekly prophylaxis may improve long-term treatment outcomes by increasing physical activity, decreasing the number of injections/treatment burden, and reducing factor consumption. Given that most haemophilia B patients follow a twice-weekly regimen, the annual number of injections could be reduced by approximately half, while maintaining potentially better protection, compared with current unmodified products.[28] Resolution of existing target joints in adolescents and adults was demonstrated in this pooled analysis, and aligns with the results of previous analyses of EHL products for long-term prophylaxis.[14] This result highlights the potential of continued, long-term N9-GP prophylaxis to minimize and possibly eliminate target joints.

Significant improvements in QoL in adolescent and adult patients were demonstrated in this pooled analysis, with EQ-5D VAS and Haem-A-QoL scores approaching those of the general population.[29] Further, the putative advantage of using the 40 IU/kg dose was strengthened by the significant improvement in Haem-A-QoL score with N9-GP 40 IU/kg versus 10 IU/kg once-weekly (P = 0.049).

The observed changes in QoL with N9-GP are likely primarily related to fewer bleeding episodes; the longer dosing interval (ie fewer injections); and/or resolution of target-joint bleeding.

With an incidence of 1:30 000, the small haemophilia B patient pool limits data collection.[30] These pooled data further support the low immunogenicity and high tolerability associated with N9-GP across all ages, as well as the efficacy particularly associated with 40 IU/kg once-weekly prophylaxis. Furthermore, in all trials in this analysis, treatment assignment was decided based on patients' individual needs; thus, the results are applicable to real-life clinical settings. Nevertheless, this pooled analysis has several limitations, including the small patient population (inherent in all trials of patients with haemophilia B) and differences in trial design and patient population between the five studies, such that not all endpoints could be reported across all trials. Further research is needed to determine whether the efficacy of once-weekly prophylaxis for haemophilia B patients translates into long-term benefits in joint outcome and QoL in children, as well as in adolescents and adults.

5 | CONCLUSION

This pooled analysis confirmed that N9-GP is well tolerated and effective in preventing bleeding at 40 IU/kg once-weekly, and maintains mean FIX activity levels ≥15% across all age groups. Once-weekly prophylaxis resolved existing target joints and improved QoL in adolescents and adults; thus, N9-GP offers excellent protection from bleeding episodes and provides a new treatment option for the prevention of bleeding in patients with haemophilia B.

ACKNOWLEDGEMENTS

We thank all investigators, study coordinators, trial staff, and especially the patients and families for participating in the trials. We thank the Novo Nordisk contributors David L. Cooper, Mirella Ezban, Yuen Man, Judi Møss, Mette Simonsen and Reto Wirz for critical review and input to the manuscript. Sola Neunie, MSc, CMPP™ (AXON Communications, London, UK) provided editorial support for the development of this manuscript.

DISCLOSURES

JO received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consultancy, and/or funds for research from Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Swedish Orphan Biovitrum. MC has received research support from Bayer, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Octapharma, Pfizer and Shire. He has also received honoraria for speaking/participating in advisory boards from Bayer, Bioverativ/Sanofi, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche and Shire. SRL has acted as a paid consultant for, and received grant/research support from Novo Nordisk. JM has received research grants from Bayer, Biogen, CLS, Sobi, Novo Nordisk and Roche, and is a member of advisory committees of Baxalta, Biogen, CSL Behring, Shire, Novo Nordisk and Roche, and speaker bureau of Amgen, Alnylam, Bayer, Biogen, Biotest and CLS. MEM has acted as consultant for Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Roche, and Baxalta/Shire, and received speaker fees from Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Roche, Octapharma, Biotest and Baxalta/Shire. TM has received research funding and honoraria from Novo Nordisk. CN has received honoraria for lectures, research and travel support or consultancy from Alnylam, Baxalta/Shire, Bayer, CSL Behring, LFB, Novo Nordisk, Octapharma and Pfizer. GY has received honoraria from Bayer, Bioverativ, CSL Behring, Novo Nordisk and Shire for consulting and speaking. WHOC and SE are employees and shareholders of Novo Nordisk A/S.

AUTHOR CONTRIBUTION

JO, MC, SRL, JM, MEM, CN and GY performed the research, were involved in the design of the study, analysed and/or interpreted the data and wrote the manuscript. TM performed the research, was involved in the design of the study, analysed and/or interpreted the data and revised the manuscript. WHOC was involved in the design of the study, analysed and/or interpreted the data and wrote the manuscript. SE was involved in the design of the study, analysed and/or interpreted the data and revised the manuscript.

ORCID

Manuel Carcao http://orcid.org/0000-0001-5350-1763
Johnny Mahlangu http://orcid.org/0000-0001-5781-7669
Guy Young http://orcid.org/0000-0001-6013-1254

REFERENCES

1. Negrier C, Knobe K, Tiede A, Giangrande P, Moss J. Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B. *Blood*. 2011;118(10):2695-2701.
2. 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(26):3880-3886.
3. Franchini M, Frattini F, Crestani S, Bonfanti C. Haemophilia B: current pharmacotherapy and future directions. *Expert Opin Pharmacother*. 2012;13(14):2053-2063.
4. Gringeri A, von Mackensen S, Auerswald G, et al. Health status and health-related quality of life of children with haemophilia from six West European countries. *Haemophilia*. 2004;10(Suppl 1):26-33.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.
6. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125(13):2038-2044.
7. Olivieri M, Kurnik K, Pfluger T, Bidlingmaier C. Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis. *Haemophilia*. 2012;18(3):369-374.

8. Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia*. 2001;7(4):392-396.
9. Miguelino MG, Powell JS. Clinical utility and patient perspectives on the use of extended half-life rFIXFc in the management of hemophilia B. *Patient Prefer Adherence*. 2014;8:1073-1083.
10. Lambert T, Recht M, Valentino LA, et al. Reformulated BeneFix: efficacy and safety in previously treated patients with moderately severe to severe haemophilia B. *Haemophilia*. 2007;13(3):233-243.
11. den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41-44.
12. Carcao M. Changing paradigm of prophylaxis with longer acting factor concentrates. *Haemophilia*. 2014;20(Suppl 4):99-105.
13. Pipe SW. The hope and reality of long-acting hemophilia products. *Am J Hematol*. 2012;87(Suppl 1):S33-S39.
14. 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(14):1761-1769.
15. Iorio A, Krishnan S, Myren K, Lethagen S, McCormick N, Karner P. Factor consumption for prophylaxis and treatment of bleeding: recombinant factor IX Fc fusion protein compared with conventional recombinant factor IX. *Value Health*. 2015;18(7):A660.
16. Powell J, Shapiro A, Ragni M, et al. Switching to recombinant factor IX Fc fusion protein prophylaxis results in fewer infusions, decreased factor IX consumption and lower bleeding rates. *Br J Haematol*. 2015;168(1):113-123.
17. Tiede A, Abdul-Karim F, Carcao M, et al. Pharmacokinetics of a novel extended half-life glycoPEGylated factor IX, nonacog beta pegol (N9-GP) in previously treated patients with haemophilia B: results from two phase 3 clinical trials. *Haemophilia*. 2017;23(4):547-555.
18. Carcao M, Zak M, Abdul Karim F, et al. Nonacog beta pegol in previously treated children with hemophilia B: results from an international open-label phase 3 trial. *J Thromb Haemost*. 2016;14(8):1521-1529.
19. Escobar MA, Tehranchi R, Karim FA, et al. Low-factor consumption for major surgery in haemophilia B with long-acting recombinant glycoPEGylated factor IX. *Haemophilia*. 2017;23(1):67-76.
20. Young G, Collins PW, Colberg T, et al. Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase III safety and efficacy extension trial (paradigm4). *Thromb Res*. 2016;141:69-76.
21. Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII: C inhibitors: improved specificity and reliability. *Thromb Haemost*. 1995;73(2):247-251.
22. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.
23. Negrier C, Young G, Abdul Karim F, et al. Recombinant long-acting glycoPEGylated factor IX (nonacog beta pegol) in haemophilia B: assessment of target joints in multinational phase 3 clinical trials. *Haemophilia*. 2016;22(4):507-513.
24. Chowdary P, Kearney S, Regnault A, Hoxer CS, Yee DL. Improvement in health-related quality of life in patients with haemophilia B treated with nonacog beta pegol, a new extended half-life recombinant FIX product. *Haemophilia*. 2016;22(4):e267–e274.
25. 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(24):2313-2323.
26. Jiménez-Yuste V, Auerswald G, Benson G, et al. Achieving and maintaining an optimal trough level for prophylaxis in haemophilia: the past, the present and the future. *Blood Transfus*. 2014;12(3):314-319.
27. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6-14.
28. Collins PW, Moss J, Knobe K, Groth A, Colberg T, Watson E. Population pharmacokinetic modeling for dose setting of nonacog beta pegol (N9-GP), a glycoPEGylated recombinant factor IX. *J Thromb Haemost*. 2012;10(11):2305-2312.
29. Miners AH, Sabin CA, Tolley KH, Jenkinson C, Kind P, Lee CA. Assessing health-related quality-of-life in individuals with haemophilia. *Haemophilia*. 1999;5(6):378-385.
30. Santagostino E, Fasulo MR. Hemophilia A and hemophilia B: different types of diseases? *Semin Thromb Hemost*. 2013;39(7):697-701.
31. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1–e47.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Oldenburg J, Carcao M, Lentz SR, et al. Once-weekly prophylaxis with 40 IU/kg nonacog beta pegol (N9-GP) achieves trough levels of >15% in patients with haemophilia B: Pooled data from the paradigm™ trials. *Haemophilia*. 2018;00:1–10. https://doi.org/10.1111/hae.13608