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ORIGINAL ARTICLE

Switching to nonacog beta pegol in hemophilia B: Outcomes from a Canadian real-world, multicenter, retrospective study

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Abstract

Background: The Canadian Bleeding Disorders Registry (CBDR) captures data from 24 hemophilia treatment centers and patients directly. Nonacog beta pegol (N9-GP) was approved in Canada in 2018.

Objectives: To assess treatment outcomes following switching to N9-GP in a real-world setting.

Methods: CBDR data for Canadian male patients (aged 7–72 years) with hemophilia B receiving prophylactic N9-GP for ≥6 months as of March 31, 2021, were included. To allow comparison with the previously used products, only patients for whom data were available in the CBDR for at least 6 months before the switch to N9-GP were included in this retrospective analysis.

Results: Forty-two patients were included in the analysis (total observation period: 148.0 patient-years). The distribution of disease severity was 62% severe, 36% moderate, 2% mild, with 62% of patients previously receiving recombinant factor IX-Fc-fusion protein (rFIXFc) and 38% previously receiving standard half-life (SHL) recombinant factor IX (rFIX). During a median follow-up period of 2.3 years on N9-GP

prophylaxis, 232 bleeds were reported in 30 patients, 29% of patients reported zero bleeds. The median overall annualized bleeding rate on N9-GP was 0.73 for patients switching from rFIXFc (previously 1.44) and 2.10 for patients switching from SHL rFIX (previously 6.06). Median total annualized factor consumption (IU/kg) was lower with N9-GP than with previous SHL rFIX (2152 vs 3018) and previous rFIXFc (1766 vs 2278).

Conclusions: Results from this first real-world study of N9-GP in patients with hemophilia B suggest optimal bleeding control with low factor consumption after switching to N9-GP, irrespective of the previous product.

KEYWORDS
Canada, hemophilia B, N9-GP, nonacog beta pegol, prophylaxis, real-world

Essentials

- Real-world study of 42 patients in Canada switching to nonacog beta pegol (N9-GP) prophylaxis.
- N9-GP treatment was compared with previously used products (standard half-life rFIX and rFIXFc).
- Post-switch to N9-GP (follow-up 2.3 years), patients experienced lower annualized bleeding rates.
- Annualized factor consumption for prophylaxis and for treatment of bleeds was reduced with N9-GP.

1 | INTRODUCTION

Prophylaxis with coagulation factor IX (FIX) is recommended for patients with severe hemophilia B and for those with nonsevere hemophilia B with a severe bleeding phenotype.[1] Traditional standard half-life (SHL) FIX concentrates require frequent infusions to achieve adequate prophylaxis and prevent bleeds. However, frequent infusions may negatively impact patient quality of life and adherence to treatment.[1] Extended half-life (EHL) recombinant FIX (rFIX) products aim to reduce the treatment burden for prophylaxis by allowing reduced dosing frequency while maintaining higher trough levels of FIX activity than are achieved with SHL FIX products.[2,3] Currently, there are three EHL rFIX products approved by Health Canada for treatment of adults with hemophilia B (nonacog beta pegol [N9-GP; REFIXIA/REBINYN; Novo Nordisk A/S, Bagsværd, Denmark]; recombinant factor IX-Fc fusion protein [rFIXFc; ALPROLIX; Sanofi Genzyme; Cambridge, MA, USA]; coagulation factor IX [recombinant], albumin fusion protein [IDELVION; CSL Behring; King of Prussia, PA, USA]); although all three show improved pharmacokinetics over SHL FIX, there are considerable differences in their pharmacokinetic profiles.[4-6]

N9-GP is a site-specific glycoPEGylated EHL rFIX product that has demonstrated safety and efficacy in patients of all age groups in the paradigm clinical development program.[4,7-11] This program focused on patients with moderate-to-severe hemophilia B who received defined dosing regimens for routine prophylaxis and treatment of bleeding episodes. There are currently no data on the clinical and economic outcomes of using N9-GP in a real-world setting. Additionally, there are no data on the real-world patterns of using N9-GP in clinical practice or on the outcomes after switching to N9-GP from a SHL FIX product or another EHL rFIX product.

In Canada, real-world data for patients with hemophilia, including clinical outcomes and consumption rates of clotting factor concentrates, are recorded in the Canadian Bleeding Disorders Registry (CBDR) by both hemophilia treatment centers (HTCs) and patients. FIX products for patients with hemophilia B are subject to national competitive procurement processes in Canada, administered by the Canadian Blood Service (CBS) and Héma-Québec.[12] As a result of a tender, rFIXFc was the only EHL FIX available to patients from 2016 to 2018. In 2018, N9-GP was awarded a CBS contract and subsequently made available to patients across Canada (except Québec) beginning April 1, 2018.[13] Patients already receiving the EHL product rFIXFc were offered the opportunity to switch to either N9-GP or the SHL product rFIX because rFIXFc was no longer available for adult patients through CBS after April 1, 2018. Patients previously on SHL rFIX and plasma-derived FIX were also able to switch to N9-GP. Recombinant FIX albumin fusion protein, although approved by Health Canada, has never been made available in the inventory of the CBS or Héma-Québec.

Currently, N9-GP is approved in Canada and reimbursed in all provinces except Québec, for routine prophylaxis in patients aged 18 years or older. It is also approved for use in pediatric patients for treatment of bleeds or prevention of bleeding in surgical settings, but not for routine prophylaxis. Despite this, the CBDR has recorded patients ≤18 years old receiving N9-GP prophylactically off-label. It is not unusual for pediatric patients to receive medications off-label because medications are often licensed in adults before being licensed in children. To increase the sample size and generalizability of the study findings, these pediatric patients have been included in the analysis. Hence, this study aimed to use the change in the CBS contract to assess treatment outcomes for patients who switched from a prophylaxis regimen with either SHL rFIX or rFIXFc to a prophylaxis regimen with N9-GP in a real-world setting.

2 | METHODS

2.1 | Study design

This was a retrospective study of Canadian patients with hemophilia B receiving prophylactic N9-GP for at least 6 months after switching from an earlier treatment product. The study was initiated on April 1, 2018, and data were collected until March 31, 2021, through the CBDR database, which records data from 24 HTCs and directly from patients. Eleven of the 24 HTCs contributed data for the purposes of this analysis (list of centers in Supplementary material 1). This pre-planned readout occurred 2 years after study initiation.

2.2 | Patient eligibility

Patients of any age with hemophilia B of any severity treated with prophylactic N9-GP for ≥6 months were included in the study. For the comparison with previously used products, only patients treated prophylactically and for whom data existed in the CBDR for ≥6 months before the switch to N9-GP were included.

2.3 | Study endpoints

2.3.1 | Primary endpoints

The primary endpoints of this study were:

a. N9-GP effectiveness for prophylaxis, described by annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR), annualized joint bleeding rate (AjBR), bleeding frequency in target joints (International Society on Thrombosis and Haemostasis [ISTH] definition: at least three spontaneous bleeds into a single joint in a 6-month period),[14] hemophilia joint health score (HJHS), and target joint progression (ISTH definition of target joint declassification: two or fewer bleeds into the joint within a consecutive 12-month period).[14] Only bleeds that required treatment were recorded in the CBDR database.
b. Total overall annualized consumption and annualized consumption for prophylaxis.
c. N9-GP consumption for surgery, described in terms of total factor consumption during surgery.

2.3.2 | Secondary endpoints

The secondary endpoints of this study were:

a. Change in ABR, AsBR, AjBR, bleeding frequency in target joints, HJHS, number of target joints, target joint progression, and number of infusions required to treat a bleeding episode, from previous FIX product to prophylaxis with N9-GP.
b. Adherence to prophylaxis, described by the number of prophylactic infusions received compared with the number of prophylactic infusions prescribed.

2.3.3 | Exploratory endpoints

The exploratory endpoints of this study describe the number and frequency of adverse events for patients receiving N9-GP.

TABLE 1 Patient demographics

	Previous SHL rFIX n = 16	Previous rFIXFc n = 26	N9-GP total N = 42
Disease severity, n (%)			
Severe	11 (68.8)	15 (57.7)	26 (61.9)
Moderate	5 (31.2)	10 (38.5)	15 (35.7)
Mild	0 (–)	1 (3.8)	1 (2.4)
Sex, n (%)			
Male	16 (100.0)	26 (100.0)	42 (100.0)
Female	0 (–)	0 (–)	0 (–)
Weight at start of N9-GP administration, kg			
Mean (SD)	78.6 (19.3)	80.1 (23.9)	79.6 (22.0)
Median (range)	80.7 (32.8–116.0)	83.4 (22.2–120.6)	82.3 (22.2–120.6)
Age group, n (%)			
<18 years	1 (6.2)	4 (15.4)	5 (11.9)
18–65 years	14 (87.5)	18 (69.2)	32 (76.2)
>65 years	1 (6.2)	4 (15.4)	5 (11.9)

Abbreviations: N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life.

2.4 | Statistics

All outcomes were reported using descriptive statistics. Specifically, measures of central tendency, dispersion indicators (mean ± standard deviation, median and interquartile range [IQR], median and ranges) and counts were used to describe the data. Data were checked for outliers in the clinical outcomes and validated clinically wherever extreme values were spotted. ABR was calculated using the formula:

$$\text{ABR} = (\text{number of bleeds} \div \text{number of days on product}) \times 365.25$$

To compare intrapatient bleed rates pre- and postswitching to N9-GP a negative binomial (NB) regression analysis was performed for each of the study groups, prior SHL rFIX, and prior rFIXFc, respectively. Estimated mean ABRs (95% confidence intervals [CIs]) before and after switching to N9-GP and corresponding rate ratio (RR) (95% CIs) were tabulated for each study group. Further, to compare intrapatient recurrent bleeding incidents between pre-N9-GP treatment and N9-GP, a shared frailty gamma model was fitted to the data for each of the study groups.[15] Estimated hazard ratios (HRs; 95% CIs, *p* values) of bleeding incidents comparing N9-GP with pre-N9-GP treatment were reported.

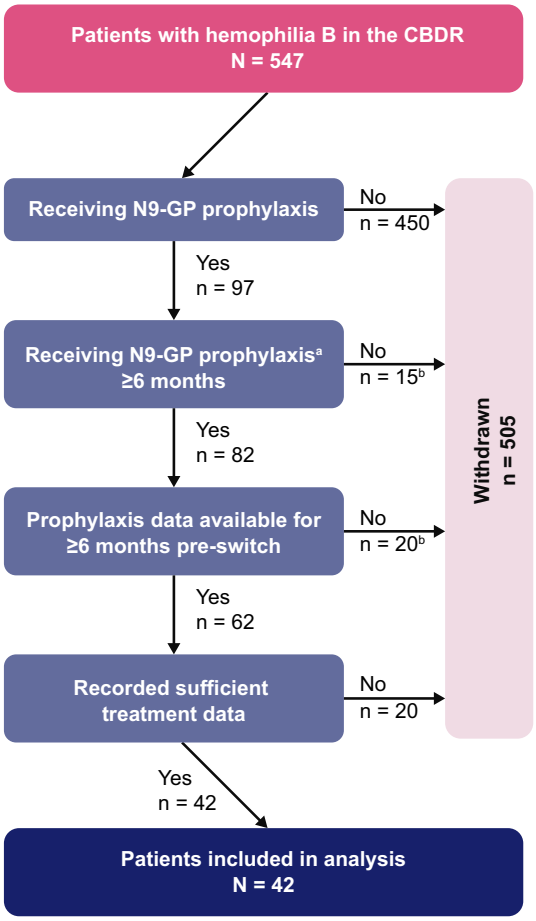

FIGURE 1 Flow diagram of patients from the CBDR included in the analyses. CBDR, Canadian Bleeding Disorders Registry; N9-GP, nonacog beta pegol. [a]As primary prophylaxis. [b]Includes one patient who received N9-GP on-demand before receiving prophylaxis for ≥3 months. [c]Includes one patient who received two products during the pre-switch period, and two patients who switched from an experimental medication

3 | RESULTS

3.1 | Demographics

Patient demographic data are presented in Table 1. At the 2-year readout (March 31, 2021), 97 patients were receiving N9-GP in the CBDR. However, only 42 male patients met the eligibility criteria and were included in the analysis (Figure 1). Eligible patients had a median age of 42 years (range 7–72), and the distribution of disease severity was 62% severe, 36% moderate, and 2% mild.

3.2 | Treatment

Before switching to N9-GP, 26 (62%) patients received rFIXFc, whereas 16 (38%) received SHL rFIX. All patients included in this analysis received previous treatment as prophylaxis. The median (range) analyzed treatment period was 1.4 (0.7–2.6) years for SHL rFIX and 1.4 (0.5–3.3) years for rFIXFc before switching, and 2.3 (0.5–3.0) years after switching to N9-GP; 26 patients completed ≥2 years on N9-GP. The combined overall observation time (pre–post switch) was 148.0 patient-years.

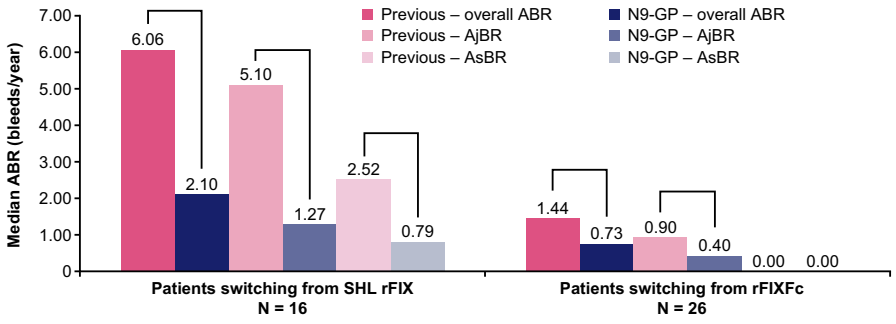

FIGURE 2 Comparative ABR, AjBR, and AsBR of prophylaxis with N9-GP versus previous products. ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate; N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life

TABLE 2 Bleeding outcomes

	From SHL rFIX to N9-GP		From rFIXFc to N9-GP			
	SHL rFIX n = 16	N9-GP n = 16	rFIXFc n = 26	N9-GP n = 26	Previous total N = 42	N9-GP total N = 42
Median (IQR) ABR						
Total	6.06 (0.83–9.80)	2.10 (0.51–4.29)	1.44 (0.40–2.95)	0.73 (0.00–1.78)	1.83 (0.43–6.30)	0.94 (0.00–2.68)
Spontaneous	2.52 (0.00–5.89)	0.79 (0.00–2.13)	0.00 (0.00–1.92)	0.00 (0.00–1.45)	0.46 (0.00–3.68)	0.40 (0.00–1.67)
Joint	5.10 (0.33–9.80)	1.27 (0.00–3.87)	0.90 (0.00–2.49)	0.40 (0.00–1.77)	1.25 (0.00–5.49)	0.48 (0.00–2.13)
Mean (95% CI) ABR						
Total	7.18 (2.87–11.48)	3.13 (1.30–4.97)	3.40 (0.49–6.31)	2.19 (0.62–3.76)	4.84 (2.44–7.23)	2.55 (1.39–3.71)
Spontaneous	4.47 (0.99–7.94)	2.03 (0.46–3.59)	2.22 (0.42–4.85)	1.11 (0.15–2.06)	3.07 (1.04–5.11)	1.46 (0.65–2.27)
Joint	5.46 (2.71–8.21)	2.61 (0.82–4.40)	3.01 (0.09–5.93)	1.62 (0.41–2.83)	3.94 (1.90–5.99)	2.00 (1.02–2.98)
Analyzed treatment period per patient, years						
Mean (SD)	1.56 (0.62)	1.77 (0.92)	1.48 (0.72)	2.16 (0.67)	1.51 (0.67)	2.01 (0.79)
Median (range)	1.39 (0.73–2.62)	2.02 (0.57–2.96)	1.35 (0.50–3.27)	2.42 (0.50–2.80)	1.35 (0.50–3.27)	2.34 (0.50–2.96)
Number of patients with bleeds, n (%)	13 (81.3)	12 (75.0)	20 (76.9)	18 (69.2)	33 (78.6)	30 (71.4)
Number of bleeds, n (%)						
Total	149	102	100	130	249	232
Spontaneous	86 (57.7)	64 (62.8)	66 (66.0)	67 (51.5)	152 (61.0)	131 (56.5)
Traumatic	56 (37.6)	33 (32.4)	28 (28.0)	48 (36.9)	84 (33.7)	81 (34.9)
Joint bleeds	122 (81.9)	88 (86.3)	84 (84.0)	98 (75.4)	206 (82.7)	186 (80.2)
Target joint bleeds	28 (18.8)	20 (19.6)	34 (34.0)	24 (18.5)	62 (24.9)	44 (19.0)
Number of bleeds treated with one infusion only, n (%)	109 (73.2)	92 (90.2)	71 (72.5)	91 (71.1)	180 (72.9)	183 (79.6)
Number of infusions required to treat a bleed						
Median (range)	1 (1–27)	1 (1–7)	1 (1–7)	1 (1–9)	1 (1–27)	1 (1–9)
Mean (SD)	2.0 (3.1)	1.3 (1.0)	1.6 (1.4)	1.4 (1.0)	1.8 (2.5)	1.4 (1.0)

	From SHL rFIX to N9-GP		From rFIXFc to N9-GP			
	SHL rFIX n = 16	N9-GP n = 16	rFIXFc n = 26	N9-GP n = 26	Rate ratio SHL rFIX to N9-GP	Rate ratio rFIXFc to N9-GP
Intrapatient ABR comparison						
Mean (95% CI)	4.32 (2.15–8.69)	2.15 (1.04–4.47)	1.52 (0.81–2.84)	0.96 (0.37–1.07)	0.50 (0.27–0.94)	0.63 (0.37–1.07)

Abbreviations: ABR, annualized bleeding rate; IQR, interquartile range; N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SD, standard deviation; SHL, standard half-life.

TABLE 3 Consumption outcomes

	From SHL rFIX to N9-GP		From rFIXFc to N9-GP			
	SHL rFIX n = 16	N9-GP n = 16	rFIXFc n = 26	N9-GP n = 26	Previous total N = 42	N9-GP total N = 42
Factor consumption per bleed, IU/kg						
Median (range)	74 (14–1447)	49 (30–525)	53 (25–449)	44 (22–404)	53 (14–1447)	45 (22–525)
Mean (SD)	107 (186)	71 (66)	81 (68)	58 (47)	97 (150)	63 (55)
Total annualized consumption, IU/kg						
Median (range)	3018 (1298–25,864)	2152 (1011–4808)	2278 (1134–6190)	1766 (900–2806)	2598 (1134–25,864)	1848 (900–4808)
Mean (SD)	4806 (5877)	2193 (1037)	2565 (1252)	1785 (590)	3462 (3930)	1948 (812)
Annualized consumption for prophylaxis, IU/kg						
Median (range)	2687 (358–23,362)	2045 (827–4122)	1961 (750–3842)	1716 (709–2425)	2357 (358–23,362)	1744 (709–4122)
Mean (SD)	4110 (5391)	1991 (867)	2180 (1030)	1630 (540)	2952 (3567)	1775 (702)
Annualized consumption to treat bleeds, IU/kg						
Median (range)	645 (26–2503)	175 (23–686)	198 (63–2250)	86 (22–1019)	287 (26–2503)	114 (22–1019)
Mean (SD)	742 (693)	244 (233)	383 (516)	239 (306)	533 (613)	241 (268)

Abbreviations: IQR, interquartile range; N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SD, standard deviation; SHL, standard half-life.

3.3 | Effectiveness

Overall median (IQR) ABR for patients switching to N9-GP prophylaxis from rFIXFc was 0.73 (0.00–1.78) bleeds/patient/year compared with 1.44 (0.40–2.95) when previously receiving rFIXFc (Figure 2); similarly, for patients who switched to N9-GP from SHL rFIX median (IQR), ABR was 2.10 (0.51–4.29) bleeds/patient/year compared with 6.06 (0.83–9.80) before switching (Figure 2). Median (IQR) and mean (CI) ABR, AsBR, and AjBR before and after switching to N9-GP are presented in Figure 2 and Table 2. Intrapatient comparison of ABR using an NB regression model demonstrated a significant reduction in ABR for patients switching to N9-GP from SHL rFIX (RR: 0.5, 95% CI 0.27–0.94, $p = 0.03$), and a nonsignificant decrease in patients who switched from rFIXFc to N9-GP (RR: 0.63, 95% CI 0.37–1.07, $p = 0.09$; Supplementary material 2). Intrapatient comparison of recurrent bleeding incidents among patients with hemophilia B demonstrated a significant reduction in recurrent bleeds for patients switching to N9-GP from SHL rFIX (shared frailty gamma model; HR: 0.38, 95% CI 0.23–0.64, $p < 0.001$) and no significant difference in patients switching from rFIXFc to N9-GP (shared frailty gamma model; HR: 0.82, 95% CI 0.48–1.40, $p = 0.47$).

Over the follow-up period, there were 232 breakthrough bleeds reported in 30 (71%) patients while on N9-GP prophylaxis (Table 2). Of the breakthrough bleeds, 186 (80%) were joint bleeds and 44 (19%) were target joint bleeds. Sixteen (38%) patients reported no joint bleeds, and 12 patients (29%) reported no bleeds at all. The median (range) number of infusions required to treat a bleed was 1 (1–9) when treated with N9-GP compared with 1 (1–27) with previous SHL rFIX and 1 (1–7) with previous rFIXFc before switching. However, the proportion of bleeds requiring only one infusion to achieve hemostasis was higher when treated with N9-GP (90.2%) compared with when the same patients were on SHL rFIX (73.2%). The proportion of bleeds treated with only one infusion was unchanged (72% vs 71%) in those patients who switched from rFIXFc to N9-GP.

Patients receiving N9-GP had fewer target joints after switching to N9-GP. Six (38%) patients previously receiving SHL rFIX had seven target joints at the onset of the study analysis period; four of them had resolution of four target joints while on N9-GP, and one patient developed one new target joint. Two patients (9%) previously receiving rFIXFc had six target joints at study onset, four of which resolved while on N9-GP, and three target joints remained in one patient.

3.4 | Factor concentrate consumption

Median (range) total annualized FIX concentrate consumption was 2152 (1011–4808) IU/kg after switching to N9-GP from SHL rFIX compared with 3018 (1298–25,864) IU/kg before; and 1766 (900–2806) IU/kg after switching to N9-GP from rFIXFc compared with 2278 (1134–6190) IU/kg before (Table 3; Figure 3). Additionally, median (range) annualized consumption for prophylaxis was 2045 (827–4122) IU/kg after switching to N9-GP from SHL rFIX compared with 2687 (358–23,362) IU/kg before; and 1716 (709–2425) IU/kg after switching to N9-GP from

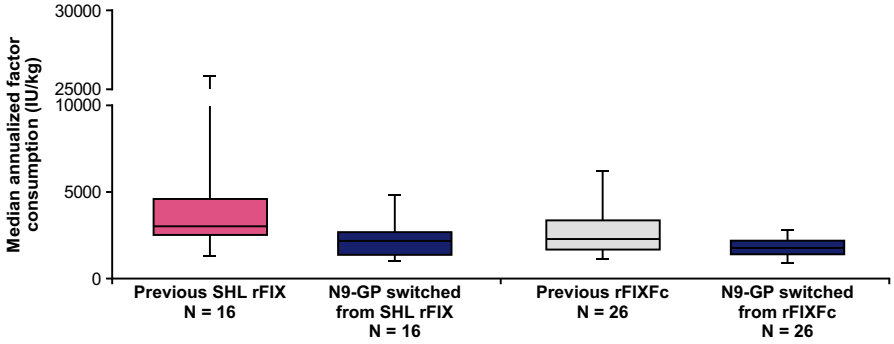

FIGURE 3 Median total annualized factor consumption after switching to prophylaxis with N9-GP compared with prophylaxis with previous products. N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life

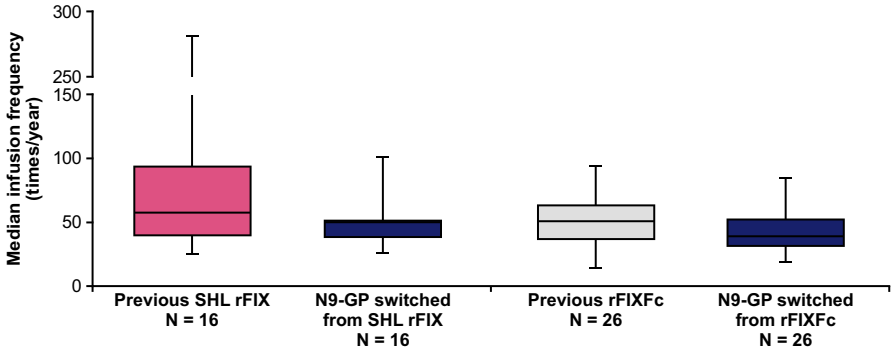

FIGURE 4 Median total annualized infusion frequency with N9-GP prophylaxis versus previous prophylaxis with previous products. N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life

rFIXFc compared with 1961 (750–3842) IU/kg before (Table 3). Median (range) consumption per bleed was 149 (23–686) IU/kg after switching to N9-GP from SHL rFIX compared with 579 (26–2503) IU/kg before and 85 (22–1019) IU/kg after switching to N9-GP from rFIXFc compared with 159 (63–2250) IU/kg before.

Annualized infusion frequency (including for prophylaxis and treatment of breakthrough bleeding) was 50.5 (26.1–100.9) after switching to N9-GP from SHL rFIX vs 57.6 (25.5–281.1) before and 39.24 (19.1–84.6) after switching to N9-GP from rFIXFc vs 51.0 (14.3–93.9) before (Figure 4). Median (range) prescribed dosing frequency was 1.0 (0.5–2.0) infusion per week with N9-GP, 2.0 (1.0–7.0) infusions per week with SHL rFIX and 1.0 (0.5–3.0) infusion per week with rFIXFc. Median (range) recorded prophylactic dosing frequency was 1.0 (0.5–1.9) infusions per week after switching to N9-GP from SHL rFIX compared with 1.1 (0.5–5.4) before switching and 0.8 (0.4–1.6) after switching to N9-GP from rFIXFc compared with 1.0 (0.3–1.8) infusions per week before.

3.5 | Surgery

There were 17 surgeries recorded while patients were receiving N9-GP, with a median (range) factor consumption during the 14-day postoperative period of 84.5 (0.0–763.0) IU/kg (Table 4).

3.6 | Safety

No adverse events were recorded in the CBDR over the course of the analysis period.

3.7 | Adult subgroup analysis

When patients ≥18 years old were analyzed separately, findings were consistent with the total study population (Supplementary material 3).

4 | DISCUSSION

Overall, the data collected from the CBDR showed a lower median ABR after switching to N9-GP compared with either previous SHL rFIX or rFIXFc, although a statistically significant reduction could be shown only for patients switching from SHL rFIX. The reduction in overall ABR was observed despite a drop in the median annualized factor consumption of 29% for patients switching from SHL rFIX and 22% for patients switching from rFIXFc. Previously, outcomes for patients in the CBDR were reported at the 1-year data readout, 1 year after initiation of the study (median [range] length of follow-up: 1.0 [0.2–1.5] years).[16] The results reported in this current study, 2 years since initiation of the study, demonstrated a similar annualized N9-GP consumption for patients who switched from SHL rFIX compared with this earlier readout (median [range] total annualized consumption of N9-GP at 1-year readout: 2146 [1084–4614] IU/kg; 2-year readout: 2152 [1010–4808] IU/kg). However, for patients switching from rFIXFc, consumption decreased further over time (median [range] total annualized consumption of N9-GP at 1-year readout: 2054 [888–3056] IU/kg; 2-year readout: 1766 [900–2806] IU/kg). This difference in consumption may have cost-effectiveness implications when comparing N9-GP with both the SHL rFIX and rFIXFc; a further analysis of cost-effectiveness in the CBDR is currently being undertaken.

TABLE 4 Surgeries

Surgical procedure (N9-GP)	Days 1–6		Days 7–13		Day 14		Total	
	No. of postoperative infusions	Consumption, IU/kg	No. of postoperative infusions	Consumption, IU/kg	No. of postoperative infusions	Consumption, IU/kg	No. of postoperative infusions	Consumption, IU/kg
Major surgeries								
Fasciotomy for compartment syndrome	7	439.3	4	185.0	2	138.7	13	763.0
Tonsillectomy, septoplasty, and bilateral inferior turbinate cauterization	6	245.8	2	59.3	0	0	8	305.1
Liver transplant	1	83.5	0	0.0	0	0	1	83.5
Minor surgeries								
Radiofrequency ablation	3	203.3	2	108.4	0	0	5	311.7
Bronchoscopy	1	63.5	3	190.5	0	0	4	254.0
Bronchoscopy	2	142.9	1	63.5	0	0	3	206.4
Corticosteroid local injection	1	48.7	1	48.7	0	0	2	97.4
Corticosteroid local injection	0	0.0	2	97.4	0	0	2	97.4
Incision and drainage right thumb cellulitis	2	94.2	0	0.0	0	0	2	94.2
Colonoscopy	1	54.7	1	29.8	0	0	2	84.5
Wisdom teeth removal	1	36.3	1	36.3	0	0	2	72.6
Dental surgery	2	72.3	0	0.0	0	0	2	72.3
Partial amputation right thumb	1	53.8	0	0.0	0	0	1	53.8
Orthopedic treatment for cubital tunnel syndrome	2	49.8	0	0.0	0	0	2	49.8
Transarterial chemoembolization for hepatocellular carcinoma	1	47.7	0	0.0	0	0	1	47.7
Wisdom teeth extraction	1	41.9	0	0.0	0	0	1	41.9
Incision and drainage left hand abscess[a]	0	0.0	0	0.0	0	0	0	0.0

Abbreviations: ABR, annualized bleeding rate; N9-GP, nonacog beta pegol; rFIXFc, recombinant factor IX-Fc fusion protein; SD, standard deviation; SHL, standard half-life.

[a]No additional doses of N9-GP were administered alongside the patients prescribed N9-GP dosing schedule.

The annualized number of recorded prophylactic infusions was lower with N9-GP than with both SHL rFIX and rFIXFc, despite being prescribed at the same infusion frequency as rFIXFc. This may suggest improvement in symptoms of hemophilic arthropathy after switching to N9-GP. In fact, four patients reported resolution of target joints following a switch from SHL rFIX to N9-GP, and two patients reported resolution of target joints in those who switched from rFIXFc. Some bleeds were still reported in patients receiving N9-GP prophylaxis. Given that the median patient age for this study was 42 years, many patients are likely to have had preexisting joint damage or target joints, which may have contributed to them continuing to report breakthrough bleeds after switching to N9-GP prophylaxis.

Following the switch from SHL rFIX to N9-GP, most bleeds (90.2%) required only one infusion to achieve hemostasis compared with 73.2% of bleeds on SHL rFIX requiring one infusion. The proportion of bleeds treated with only one infusion remained stable (72% vs 71%) following the switch from rFIXFc to N9-GP. The finding that >90% of bleeds treated with N9-GP needed only one infusion of N9-GP to achieve hemostasis is consistent with the hemostatic efficacy observed in the paradigm trials with N9-GP (40 IU/kg once weekly).[4,7,9,17]

Interestingly, ABR outcomes were lower in the cohort that switched to N9-GP from rFIXFc than in the cohort that switched to N9-GP from SHL rFIX. Over time, with further follow-up on N9-GP, these rates may become more similar; in fact, when comparing the outcomes reported at this 2-year readout with those previously reported at the earlier 1-year readout,[15] a decrease is observed across all ABR measures. The analysis of intrapatient bleeding rates allowed for effective comparison of ABR despite the imbalance in follow-up periods, the robustness of these findings was confirmed by using both the NB regression and shared frailty gamma models.

The improvements in ABR and consumption outcomes observed after switching from rFIXFc to N9-GP might be due to the high trough levels observed between doses of N9-GP, which may in turn confer a protective effect.[18] Additionally, adherence to prophylactic SHL rFIX appeared lower than with either rFIX-Fc or N9-GP. The effects of more consistent prophylaxis may not fully manifest until years after switching to an EHL product.

Because the switch from rFIXFc was due to the product no longer being provided under the CBS contract (though still available via Health Canada's special access program) rather than because of inadequate disease control, the 1.35-year follow-up period was likely representative of the overall patient experience on rFIXFc. However, because access to SHL rFIX was unaffected by CBS contracting changes, the patients who switched from SHL rFIX may be a self-selected group whose disease was not adequately controlled by their prior treatment.

Given the small sample size and self-reporting nature of this retrospective study, insufficient data were available to report on all the planned endpoints set out in the study protocol. However, it is anticipated that sufficient data will be available to report on these additional endpoints at subsequent data readouts. The small sample size is the main limitation of this study. This limitation is common among hemophilia B studies given the rarity of the disease. Additionally, CBDR data are collected as part of routine clinical practice, and therefore data are not always optimally complete or standardized; this was further compounded by the COVID-19 pandemic in 2020, which limited attendance at hemophilia clinics for physical examinations. For example, for the endpoint HJHS, insufficient data were available (4/42 patients) to power a meaningful analysis. Because the study was retrospective and non-interventional, it was not possible to audit patients for their data entry activity for the purposes of the study. According to the CBDR's standard data quality improvement initiative, investigators were able to encourage the HTCs and their patients to be as compliant as possible when entering data into CBDR, but the data collection activity remained completely voluntary.

5 | CONCLUSION

In summary, this study provided the first report of the efficacy and safety of N9-GP in a real-world setting. The results of this study suggest that N9-GP compares favorably with both SHL rFIX and rFIXFc in terms of improved bleeding outcomes and reduced rFIX consumption.

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RELATIONSHIP DISCLOSURES

D.M. has received research support from Bayer, Bioverativ/Sanofi, and Pfizer; and honoraria for speaking/participating in advisory boards from Bayer, Bioverativ/Sanofi, BIOVIIIx, Pfizer, and Sigilon. A.I.'s institution has received project-based funding via research or service agreements with Bayer, CSL, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, and Takeda. F.G.'s institution has received research support from BioMarin, CSL, Freeline, Grifols, Novo Nordisk, Octapharma, Sanofi, Spark, and Uniqure. A.C. is an employee of Novo Nordisk. M.C. has received research support from Bayer, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Shire/Takeda and honoraria for speaking/participating in advisory boards from Bayer, Biotest, Bioverativ/Sanofi, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire/Takeda. J.H.-G. has received research support from Bayer and Novo Nordisk. P.J. has received research funding from Bayer, CSL Behring, and Takeda. A.L. has received research grants from Bayer and Bioverativ/Sanofi and was a speaker/participant in advisory boards for Bayer, Novo Nordisk, Pfizer, and Shire/Takeda; ad hoc speaker

for Bayer, Novo Nordisk, and Pfizer; attended advisory board meetings of Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Pfizer, Roche, and Takeda; and received grant funding from Bayer and CSL Behring. C.W.P. has received honoraria for participating in advisory boards and travel support from Alexion, Amgen, AstraZeneca, Bayer, Bioverativ/Sanofi, Bristol Myers Squibb/Celgene, Gilead, Janssen, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, Shire/Takeda, and Teva. H.S. has received honoraria for participating in advisory boards from Novo Nordisk, Octapharma, and Sanofi and research support from Octapharma. J.T. has been a consultant and served on advisory boards and data monitoring committees for Bayer, BioMarin, Novo Nordisk, Octapharma, Pfizer, Roche, and Takeda. M.-C.P. has received grant funding from Bayer and CSL Behring; ad hoc speaker for Bayer, Novo Nordisk, and Pfizer; attended advisory board meetings of Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Pfizer, Roche, and Takeda. A.K. and E.I. have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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