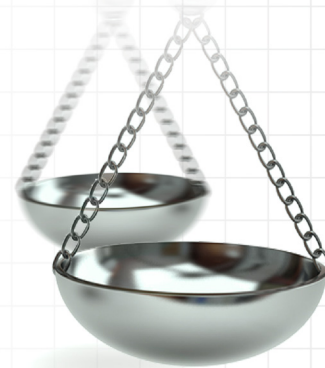




A new modeling approach allowing prediction and comparison of the long-term outcomes of treatments for hemophilia B

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Aim: To develop a modeling approach to compare clinical outcomes of nonacog beta pegol to a standard-acting factor IX (FIX) product. **Methods:** Regression analysis linked FIX activity to bleed rates. Pharmacokinetic parameters were used to estimate FIX activity over time. The probability of bleeds was estimated for both treatment arms. A Markov model estimated the presence of target joints and annualized bleed rates (ABRs). **Results:** Higher FIX activity showed reduced ABRs ($p < 0.001$). Target joints resulted in higher bleed rates ($p < 0.001$). When FIX activity levels and bleed risks were applied to the Markov model, ABRs for nonacog beta pegol and its comparator were 2.40 and 6.36, respectively. **Conclusion:** This model provides a starting point for assessing the added value of new FIX products.

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Keywords: alternative indirect treatment comparison • factor IX • hemophilia B • modeling • nonacog beta pegol • pharmacokinetics • prophylaxis

Treatment of hemophilia B requires factor replacement therapy with factor IX (FIX) containing concentrates to supplement FIX activity levels, which are reduced in hemophilia B patients. FIX can be administered prophylactically or for treatment of bleeding episodes, depending on individual patient's needs and/or product availability. In addition, FIX is used during and after surgery in hemophilia patients [1,2]. Until recently, treatment options have been limited to FIX products with similar pharmacokinetic (PK) characteristics. Because these products are similar, assessing the differences in efficacy and cost-effectiveness between them has not been necessary. Furthermore, current hemophilia treatment guidelines do not recommend certain products over others [2–6].

Recently, a wider range of products have become available for the treatment of hemophilia B [7]. These products, especially those with extended half-lives (EHLs), may provide additional value in the treatment of hemophilia B [8–10]. The newly available products with EHL have the potential to decrease the frequency of prophylaxis (PPx) dosing while simultaneously maintaining patients at higher FIX activity levels between doses. This is an important improvement in the treatment of hemophilia B, which is supported by guidance issued by the EMA, stating that appropriate PK data are the most important surrogate end points for the assessment of efficacy of new FIX products. The same guidelines dictate that treatment should aim to maintain high levels of FIX activity. FIX activity levels are directly correlated to percentages of factor level; for example, 1 IU/dl represents 1% and 5 IU/dl represents 5% [1]. FIX activity levels <1 IU/dl are classified as severe hemophilia B; levels of 1–5 IU/dl represent moderate hemophilia B; levels of 5–40 IU/dl represent mild hemophilia B; and levels over 40 IU/dl are seen as normal FIX activity levels [1].

Table 1. Paradigm™ trial outcomes.							
Trial arm	Number of patients	Total patient years	Total bleeds	ABR	TJs at baseline, n	TJs resolved, n (%)	New TJs, n
OD	15	7.73	143	18.5	20	5 (20%) [†]	4
PPx, 10 IU/kg	30	28.97	143	4.56	24	7 (29%)	5
PPx, 40 IU/kg	29	27.91	70	2.51	24	16 (67%)	0

[†] OD patients were followed up for 6 months, while PPx patients were followed up for 12 months.
ABR: Annualized bleed rate; IU/kg: International unit per kilogram; OD: On demand; PPx: Prophylaxis; TJ: Target joint.
Data taken from [8].

In current developed markets, where products are now available with different properties and thus different expected efficacies, payers may request an assessment of the differences between the alternatives available. However, due to the variability in patient responses and no previous requirement for comparative data in guideline development, these different products have not been compared directly in head-to-head trials. Indeed, to our knowledge, no direct or indirect comparison of the efficacy and long-term outcomes of different FIX products has previously been performed.

Given the lack of comparative evidence, mathematical modeling may be useful for comparing different FIX products. A link between FVIII activity levels and bleed risk has been suggested in patients with mild-to-moderate hemophilia A treated on demand [11–13]. If such a link also exists in hemophilia B, it may be used to predict the efficacy of different products, based on estimating the risk of bleeding at different FIX activities between doses. This risk can be estimated using dosing schedules and PK parameters. This link has previously been hypothesized in hemophilia B but has not yet been established [14]. However, outcomes for the EHL product nonacog beta pegol (N9-GP) indicate such a relationship (Table 1) [8].

Our objective was to develop a method for comparing the relative efficacy of different FIX products to form the basis for a model that meets payers’ demands for comparative evidence. This article describes the developed method, using an example comparing N9-GP (a FIX product with EHL) to a standard-acting FIX product.

Methods

To predict long-term health outcomes of hemophilia B patients via an indirect treatment comparison, three levels of modeling were undertaken: first, pharmacodynamic modeling to estimate the link between FIX activity and bleeding frequencies; second, PK modeling to predict FIX activity levels in patients with regular PPx treatment; and third, Markov modeling to estimate the impact of the above on the cumulative number of bleeds and joint status over time.

Correlating FIX activity levels to bleeding risk for N9-GP

Patient levels of FIX activity over the 1-year time course of Paradigm™2 (the pivotal trial of the Paradigm N9-GP clinical trial program) were not measured continuously but were predicted from patients’ dosing diary records, using published PK parameters observed from single doses in the trial [15]. These profiles of predicted FIX activity over time were superimposed upon the bleeding episode records in the same diaries, thus establishing a correlation between annualized bleed rates and FIX activity levels. No patient-level data for the comparator treatment were used, as these were not available to the authors.

A regression analysis was done using a negative binomial model. Poisson and negative binomial distribution models are the most widely used in the analysis of count data, such as bleeding episodes [16]. However, when the duration of observation is relatively short versus the frequency of events, count data become right-skewed (the mean number of events is typically greater than the median) with a large proportion of zeros, which is relevant to the bleeding data presented here [11]. Thus, the Poisson distribution assumption that the mean and variance of the data are approximately equal is violated, and it is deemed appropriate to account for overdispersed data by employing a negative binomial regression, which was done in this analysis. The negative binomial model structure has previously been used in hemophilia trials for annualizing bleed data [11].

Negative binomial regression models were fit to assess the number of total, joint, spontaneous and traumatic bleeding episodes within FIX activity level categories, adjusted for age and whether patients had target joints (TJs). The FIX activity level categories were chosen based on clinical guidance (> 50 IU/dl [normal], 20–50 IU/dl [mild to normal], 10–20 IU/dl [mild], 5–10 IU/dl [mild], 1–5 IU/dl [moderate] and ≤1 IU/dl [severe], representing

Table 2. Pharmacokinetic parameters for nonacog beta pegol and a standard-acting factor IX product.

FIX product	Parameter	Value in standard units	Standard units	Ref.
N9-GP	MRT	156.1	h	[15]
	Vss	65.6 [†]	ml/kg	
	CL	0.42	ml/h/kg	
Standard-acting FIX product	MRT	32.24	h	[17]
	Vss	220	ml/kg	
	CL	6.81	ml/h/kg	

[†]Not reported, calculated from Vss = MRT × CL.

CL: Clearance rate; FIX: Factor IX; h: Hour; kg: Kilogram; ml: Milliliter; MRT: Mean residence time; N9-GP: Nonacog beta pegol; Vss: Volume at steady state.

Table 3. Changes in target joints in Paradigm™2.

Trial arm	Total patients (N)	At baseline		After 1 year		Probabilities	
		<i>n</i> with ≥1 TJ	Total TJs	<i>n</i> from ≥1 to 0 TJ	<i>n</i> from 0 to ≥1 TJ	from ≥1 to 0 TJ	from 0 to ≥1 TJ
10 IU/kg	30	13	24	1	1	0.08	0.06
40 IU/kg	29	15	24	9	0	0.6	0

IU/kg: International unit per kilogram; n: Number; TJ: Target joint.

Data taken from [19].

compromises between clinical traditions and the FIX activity levels most frequently present within our data). Since each patient has multiple records, a random effect for patient ID was used in the model to account for the correlation between observations within a given patient. The fitted regression models based on Paradigm2 patient level data were applied to both arms of the Markov model.

Simulating different PPx regimens

Published PK parameters for N9-GP and for standard-acting FIX products were used to predict FIX levels over time profiles for patients treated with the respective FIX products for the purpose of predicting their bleed rates (Table 2) [15,17]. For simplicity and comparability, it was assumed that both products followed a one-compartmental PK profile. Continuous treatment with a once weekly dose of 40 IU/kg was assumed for patients treated with N9-GP, and a dose of 40 IU/kg every 3.5 days was assumed for patients treated with the comparator treatment [15,18].

From these predicted FIX activity levels, the amount of time spent in each of the six categories of FIX activity levels over the course of a day was estimated. With that, the probability of experiencing a bleed was calculated using the regression analyses discussed above for total, joint, traumatic and spontaneous bleeds, from which the predicted annualized bleed rate could be calculated; see the Supplementary Information for an example calculation of the daily probability of experiencing a bleed.

Correlating bleed rates to TJ status for N9-GP

Curves were fit to estimate the correlation between the probabilities of changes in joint status in Paradigm2, as presented in Table 3, and the predicted joint bleed rates, to model the probability of developing new TJs or joints, no longer being considered TJs for both patients treated with N9-GP and the standard-acting FIX product.

Markov modeling

To predict the long-term outcomes of patients with hemophilia B treated prophylactically with N9-GP compared with a standard-acting FIX product, a Markov model structure was developed that tracked a simulated cohort of patients over time (Figure 1). Disease progression was modeled using the presence of and change in the number of TJs. The Markov model input values are provided in Table 4. A Markov cycle length of 1 month was adopted in which patients can move between the different health states. 1-year and 5-year time horizons of the model were explored.

Transitioning between the health state of no TJs and one or more TJs is partly based upon a natural increase and decrease in TJs, and partly upon resolving TJs through surgery. Multiple definitions exist for TJs as well as for the case when a joint is no longer considered a TJ [2,8,22–25]. The definition of a new TJ used in this analysis is three or more bleeds in the same joint within 6 months [2,8]; a joint is no longer considered a TJ if no bleeds have occurred

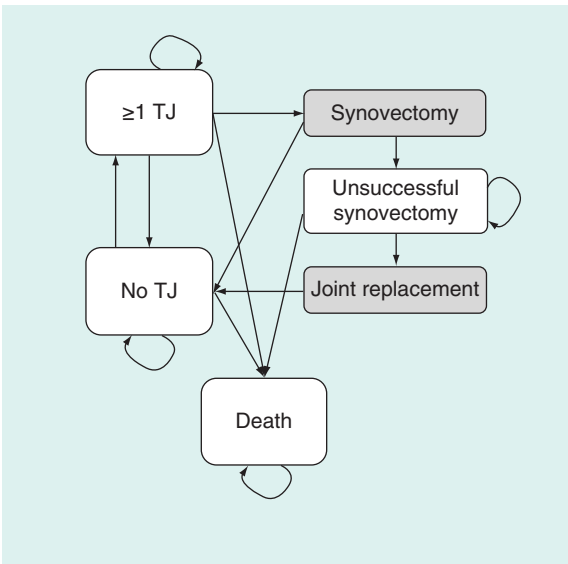


Figure 1. Markov model structure. TJ: Target joint.

Table 4. Markov model parameters.		
Parameters	Value used in the model	Source
Baseline patient characteristics		
Age	31 years	Paradigm™2
Weight	73.7 kg	Paradigm2
No TJ	46%	Paradigm2
≥ 1 TJ	54%	Paradigm2
Probabilities		
Probability bleed is severe	0.005	Paradigm2
At 12 months, probability of going from ≥ 1 to 0 TJ – N9-GP 40 IU/kg once weekly	0.60	Paradigm2
At 12 months, probability of going from 0 to ≥ 1 TJ – N9-GP 40 IU/kg once weekly	0.00	Paradigm2
At 12 months, probability of going from ≥ 1 to 0 TJ – standard-acting FIX product 40 IU/kg twice weekly	0.06	Calculated
At 12 months, probability of going from 0 to ≥ 1 TJ – standard-acting FIX product 40 IU/kg twice weekly	0.07	Calculated
Monthly probability of synovectomy	0.004	O'Hara [20]
Probability synovectomy is successful	0.75	Rodrigues-Merchan and Wiedel [21]
Monthly probability of joint replacement surgery	0.011	O'Hara [20]
FIX: Factor IX; IU/kg: International unit per kilogram; TJ: Target joint.		

into the joint over a 12-month period [8]. The resolution and development of TJs in the comparator arm were based on an assumption that the number of TJs correlates with the number of joint bleeds (Figure 2 & Table 4). The probabilities of resolving or developing TJs are equal in subsequent years, as only data for 1 year were available.

Patients with at least one TJ are considered at risk of undergoing a synovectomy to treat their TJ [21]. If the synovectomy is successful, the patient moves to the ‘no TJ’ health state. If the synovectomy is unsuccessful, the patient moves into the ‘unsuccessful synovectomy’ health state, where they are at risk of joint replacement surgery. After joint replacement surgery, the patients move to the ‘no TJ’ health state. Probabilities used in the model are presented in Table 4.

Results

Associating FIX activity levels & other prognostic factors with bleeding risk for N9-GP

For those patients for whom FIX activity levels were measured in Paradigm2, there was a strong positive correlation ($r = 0.88$; $p < 0.001$) between the observed and calculated FIX activity levels (Supplementary Figure A).

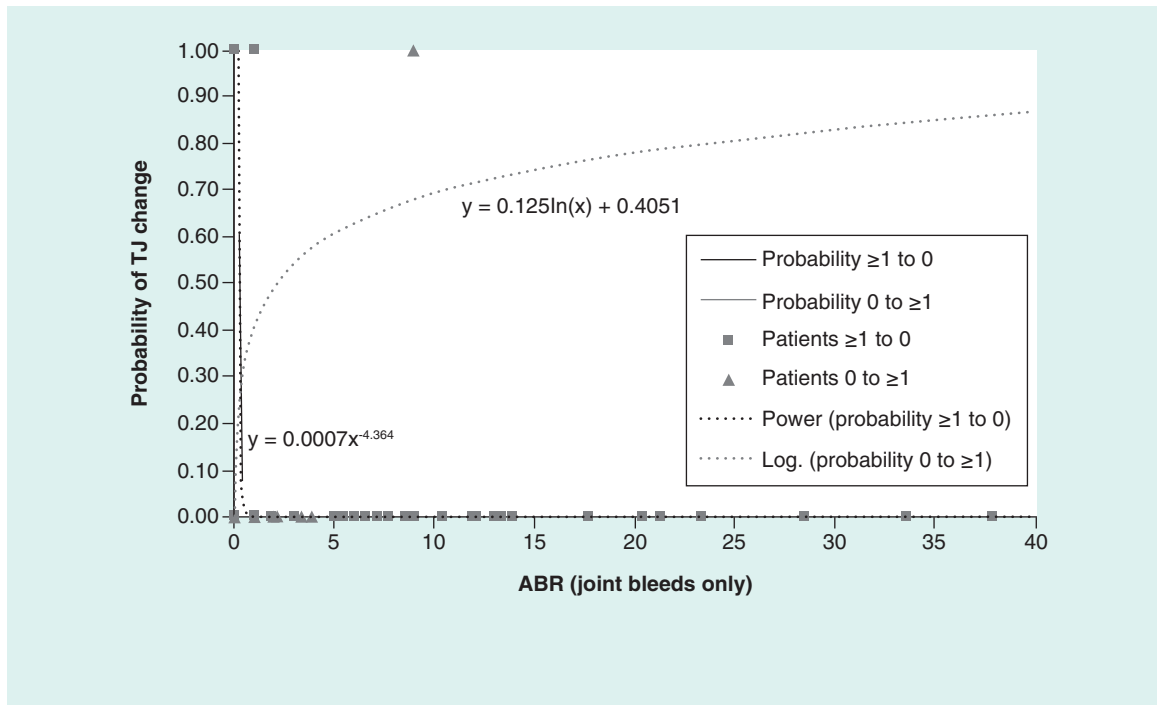


Figure 2. Probability of change in target joint status by annualized joint bleed rate.
ABR: Annualized bleed rate; TJ: Target joint.

The regression analyses linking FIX activity levels to bleed rates show that FIX activity has a statistically significant impact on the rate of bleeding episodes (at a 5% significance level for all FIX activity level categories) compared with FIX activity levels >50 IU/dl, and that patients with at least one TJ have a significantly higher rate of bleeding episodes compared with patients who have none. Age has no statistically significant effect ($p = 0.657$) on the rate of bleeding episodes. Detailed results of these analyses are presented in Supplementary Table A.

Simulating different PPx regimens: FIX activity levels over time

Calculated FIX activity levels based on published PK information show higher FIX activity levels over time for patients treated with N9-GP 40 IU/kg once weekly compared with 40 IU/kg twice weekly for the standard-acting FIX product (Figure 3). Modeled peak FIX activity levels are 92.6 and 19.6 IU/dl, respectively, and modeled trough levels are 31.8 and 1.5 IU/dl, respectively.

Simulating different PPx regimens: bleeding risk over time

The pharmacodynamic and PK modeling results were combined in calculating the probability of experiencing a bleed over time (Figure 3). The annual probability of experiencing a bleed ranges between 0.56 and 1.49 for N9-GP and 1.60 and 4.65 for the standard-acting FIX product. Calculated monthly probabilities of experiencing a bleed are presented in Table 5.

Correlating bleeding rates to TJ status for N9-GP

Curves were fit to the data presented in Table 3 and the predicted monthly joint bleed rates (Figure 2). As the number of joint bleeds per year increases, the probability of going from one or more TJs to no TJ decreases, while the probability of going from none to at least one TJ increases. These curves were applied to the calculated joint bleed rates for both model arms to predict the probability of change in joint status.

Simulating different PPx regimens: TJ status over time

Using outcomes from the pharmacodynamic and PK modeling, it was shown that the average number of bleeds at the end of the 1-year time horizon experienced by N9-GP patients was 2.40 bleeding episodes, while patients treated with the comparator product experienced 4.47 bleeding episodes. At the end of the 5-year time horizon,

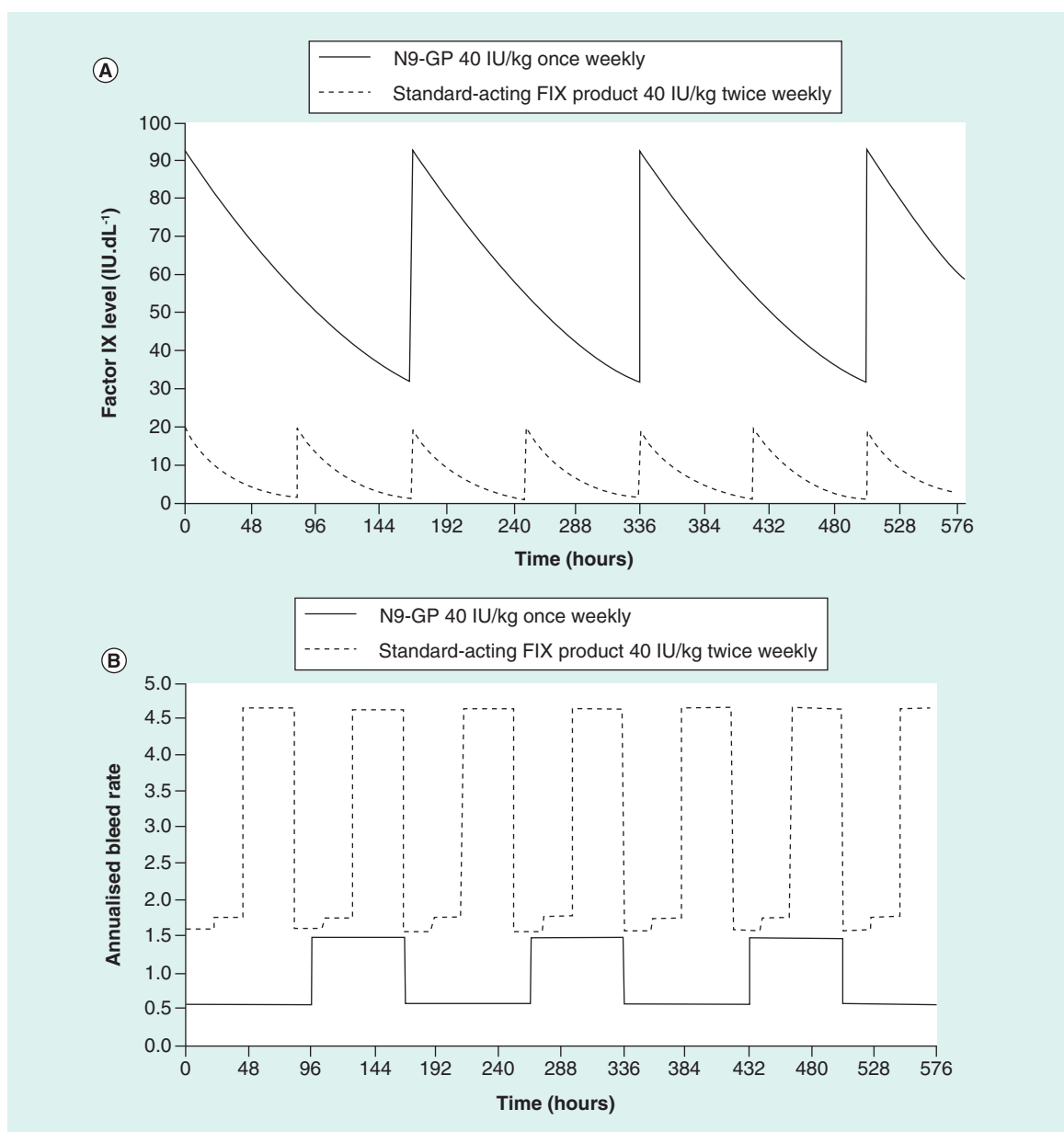


Figure 3. Calculated factor IX activity level and probability of bleed over time. **(A)** Calculated FIX activity level over time profiles for N9-GP and a standard-acting FIX product; **(B)** the probability of bleed over time for a patient without TJs. For N9-GP, a once-weekly dose of 40 IU/kg is assumed; for the standard-acting FIX product a twice weekly dose of 40 IU/kg is assumed [8,18]. This analysis is based on a one-compartmental pharmacokinetic model for both products. FIX: Factor IX; IU/kg: International unit per kilogram; N9-GP: Nonacog beta pegol; TJ: Target joint.

taking into account the change in TJ status, the average total number of bleeds experienced was 7.29 and 21.96 for N9-GP and the standard-acting FIX product, respectively (Table 6). After 5 years, the proportion of patients alive with at least one TJ were 0.4 and 47.5% for the respective model arms (Table 6).

Discussion

The current model serves as a starting point for assessing the added value of new products coming to the market for the treatment of hemophilia B. Lacking a direct comparative trial, the approach assumes that PK data may be less dependent on trial-specific circumstances than efficacy data. Therefore, this approach predicts the efficacy of different FIX products based on the observed link between PK and efficacy for one of them (N9-GP) combined

Table 5. Monthly probabilities of bleeds.

Health state	Total bleeds	Joint bleeds	Traumatic bleeds	Spontaneous bleeds
Treated with N9-GP 40 IU/kg once weekly, no TJ	0.079	0.039	0.040	0.020
Treated with N9-GP 40 IU/kg once weekly, ≥ 1 TJ	0.304	0.216	0.094	0.126
Treated with standard-acting FIX product 40 IU/kg twice weekly, no TJ	0.148	0.067	0.033	0.054
Treated with standard-acting FIX product 40 IU/kg twice weekly, ≥ 1 TJ	0.566	0.370	0.078	0.333

FIX: Factor IX; IU/kg: International unit per kilogram; N9-GP: Nonacog beta pegol; TJ: Target joint.

Table 6. Clinical Markov model outcomes at a 1-year and 5-year time horizon and mean ABRs reported in the literature.

Outcome	Mean ABR reported (95% CI)		Cumulative after 1 year		Cumulative after 5 years	
	N9-GP [8]	Standard-acting FIX product [21]	N9-GP	Standard-acting FIX product	N9-GP	Standard-acting FIX product
ABR total bleeds	2.51 (1.42–4.43)	2.6 (-0.1 to 5.3)	2.40	4.47	7.29	21.96
ABR joint bleeds	1.94 (0.98–3.82)	1.9 (SD: 4.5)	1.61	2.76	4.33	13.52
ABR traumatic bleeds	1.29 (0.76–2.19)	1.3 (SD: 2.4)	0.82	0.69	2.99	3.41
ABR spontaneous bleeds	1.22 (0.48–3.10)	1.7 (SD: 2.4)	0.93	2.44	2.41	11.96
Synovectomies	N/A	N/A	0.03	0.03	0.04	0.13
Joint replacement surgeries	N/A	N/A	0.00	0.00	0.01	0.03
Proportion of alive patients with ≥ 1 TJ	N/A	N/A	20.8%	52.5%	0.4%	47.5%

For N9-GP, a once-weekly dose of 40 IU/kg is assumed; for the standard-acting FIX product a twice-weekly dose of 40 IU/kg is assumed [8,18].

ABR: Annualized bleed rate; FIX: Factor IX; N9-GP: Nonacog beta pegol; N/A: Not applicable; SD: Standard deviation; TJ: Target joint.

with the PK properties, and labeled dosing regimens for the standard-acting product; this allows an alternative way of indirect comparison between different FIX products for the prophylactic treatment of hemophilia B.

The regression analysis on N9-GP patient-level data implies a statistically significant relationship between FIX activity level and the probability of experiencing bleeds. This exposure–response relationship, assumed to apply equally to the different products uses, causes the number of expected bleeds over time to be higher for the standard-acting FIX product compared with N9-GP. This, in turn, results in better long-term outcomes for N9-GP regarding the proportion of patients with TJs and the number of surgeries required to treat TJs.

While the model reproduces the N9-GP trial bleeding data well [8], the agreement with the reported data for standard-acting FIX products is not so good. However, the model predictions do fall within the 95% CI reported [26]. It was expected that the model would better reproduce the N9-GP than the comparator data, as the regression analysis only included patient-level data for patients treated with this product and not with a standard-acting FIX product. Another reason may be simplification of the model by using a one-compartmental PK model for all products.

Furthermore, the assessment of bleeds is performed by patients and is thus subjective; this, among other things, makes results from different trials less comparable. Many episodes that are reported as a joint bleed might actually be pain from chronic arthropathy that is misinterpreted by the patient [27,28]. This could explain the reporting of spontaneous bleeds in the trial for N9-GP, which occurred despite patients having normal FIX activity levels. Additionally, the relatively high traumatic bleed rates that were reported may be due to patients being more active because they feel better protected due to higher FIX activity levels (which could result in improved health-related quality of life); however, there are no data available to confirm this causality. Such limitations will be difficult to overcome until more objective ways of assessing bleeds are identified.

The big difference in number of bleeds between the two products after 5 years is partly due to the expected difference in the number of TJs in the two populations. A part of the difference may however also be explained by the high level of uncertainty in the current analysis. Apart from the uncertainties already discussed, the Paradigm2 trial

had a treatment duration of only 1 year. All estimates made in the model beyond 1 year are based on extrapolation of the available data and the assumption that bleed rates and probabilities of resolving or developing TJs are constant over time.

Patients treated prophylactically with N9-GP only spend a very limited time at low FIX activity levels (<5 IU/dl, no patient in Paradigm2 treated prophylactically with 40 IU/kg once weekly had any FIX activity levels <5 IU/dl). Therefore, the number of observations from PPx patients alone at the lower FIX activity levels is limited, and thus, the rate of bleeding at low FIX activity levels could not be accurately estimated. To provide a more accurate estimate of bleeding rates associated with low FIX activity levels, the patients in the clinical trial that was treated on demand were also included in the analysis, although they were not randomized to be treated in this way. This is an important limitation of the analysis, as the nonrandomization of patients over the arms may have introduced bias.

In this model, a fixed-dosing schedule is used, as described in the label of the products. It has been suggested that this may not represent dosing in clinical practice, which may deviate from that prescribed in the label. However, as there are insufficient data on actual dosing regimens, we assumed that the average dosing schedule is similar to the prescribed schedule [29–31]. Furthermore, some dosing regimens of EHL products focus on sustaining higher FIX levels, while others focus on extending the interval between doses. This can be seen as a trade-off between protection and convenience. Therefore, the efficacy modeled in the current model is largely dependent on the dosing regimen assumed, and could thus be different from the efficacy in clinical practice.

Conclusion

The current model can serve as an example of a tool to assess the potential differences between FIX products in the new era of improved patient choice. It is the first attempt at closing the gaps between the available evidence and the evidence required for potential future payer assessments. The validity of the model can be improved as more data become available to base assumptions on. In particular, quantifying the link between FIX activity levels and bleed risk requires further research. It is also important that there is a continuous focus on the standardization of end points across clinical trial programs in hemophilia, such as the alignment around the assessment of TJs and the method for reporting bleeds. We believe that, once more robust data are available, a model such as the current one could also be used to assess differences between multiple EHL products. This type of model could potentially also be used for hemophilia A, where there is a similar lack of comparative evidence.

Summary points

- There are a lack of head-to-head comparisons between factor IX (FIX) products used for the prophylactic treatment of hemophilia B to prevent bleeding episodes, and therefore, payers struggle to assess the relative clinical value of new products.
- We aimed to develop a modeling approach to compare the clinical outcomes of nonacog beta pegol (N9-GP) with a standard-acting FIX product.
- Patient-level data for N9-GP were used to link FIX activity levels to bleed rates, and published PK parameters were used to estimate FIX activity over time for patients treated with either N9-GP or the comparator.
- From these, the probability of experiencing a bleed was estimated for both treatment arm, which was used as an input for a Markov model, estimating the presence of target joints (TJs), and annualized bleed rates (ABRs) over a 5-year time horizon.
- Higher FIX activity levels showed statistically significantly reduced ABRs ($p < 0.001$).
- Patients with ≥ 1 target joints showed significantly higher bleed rates compared with patients with none ($p < 0.001$).
- When FIX activity levels and bleed risks were applied to the Markov model, estimated mean ABRs for N9-GP and its comparator were 2.40 and 6.36, respectively.
- Despite the absence of direct comparative data, modeling can be used to compare the long-term effectiveness of FIX products.
- The current model provides a good starting point for assessing the added value of new products coming to the market, and can be improved as more data become available.

Financial & competing interests disclosure

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are employees of Novo Nordisk A/S. M van Keep and M Hemstock are, and C Knight was, employees of BresMed, which was paid by Novo Nordisk A/S to conduct this research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Study Paradigm™2 was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical practice. For trial sites in the USA, the 21 Code of Federal Regulations parts 312, 50 and 56 were followed. The study protocol and amendments were reviewed and approved according to local regulations by appropriate health authorities, and by independent ethics committees/Institutional Review Boards.

Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Informed consent was obtained after the study was fully explained and before the performance of any study-related activity.

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