Journal of Blood Medicine

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RESEARCH LETTER

Efficacy of EHL N9-GP for on-demand treatment of bleeding episodes in hemophilia B: analysis of pivotal trial data

This article was published in the following Dove Press journal:
Journal of Blood Medicine

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The safety and efficacy of N9-GP (nonacog beta pegol; Novo Nordisk A/S, Bagsværd, Denmark), a recombinant glycoPEGylated factor IX (FIX) with extended half-life (EHL),[1] was investigated in the multinational, Phase 3, paradigm 2 trial (NCT01333111), previously reported by Collins et al in *Blood*.[2] The trial was conducted in accordance with the Declaration of Helsinki and written informed consent was provided by all participants. Prior to trial initiation, the protocol, the protocol amendments, the consent form, and the patient information sheet were reviewed and approved according to local regulations by appropriate health authorities and by independent ethics committees/institutional review boards (see Table S1). Patients 13–70 years of age with previously treated hemophilia B (≤2% baseline FIX) were allocated to either once-weekly prophylaxis or on-demand (OD) treatment. The OD treatment was a US Food and Drug Administration requirement prior to enrolling patients on prophylaxis in the USA.

While much of the focus on EHL FIX products has been around prophylaxis, some patients with severe hemophilia, and the majority with mild/moderate hemophilia, are treated OD. Recent epidemiologic studies have demonstrated that patients with FIX levels up to 15–20% may experience bleeding.[3,4] Thus, renewed interest in the potential use of N9-GP as a single-dose OD treatment prompted a post hoc patient-level analysis from the paradigm 2 trial to describe the dosing and efficacy of N9-GP as an OD treatment.

Fifteen of 74 patients in paradigm 2 were enrolled to OD treatment, consisting of a single 40-IU/kg dose of N9-GP, with additional doses of 40 IU/kg as required. Thirteen patients (86.7%) had severe hemophilia (FIX <1 IU/dL) and 2 (13.3%) had moderate hemophilia (FIX 1–2 IU/dL). Twelve patients (80.0%) had target joint (TJ) bleeds at baseline. The study duration of OD treatment in paradigm 2 was 28 weeks.

Fourteen patients reported 143 bleeds, all mild/moderate in severity (Table 1). Most bleeds (83.9%) were treated with a single dose of N9-GP, and the remainder with 2 or more doses (Table 1). Considering patient-level data, seven patients had all 62 of their bleeds (100%) treated with 1 dose. Annualized bleeding rates in these patients were reduced by 37% from 26.1 prestudy to 16.5 on-study. Hemostatic response was rated excellent for 36 and good for 26 bleeds.

The other seven patients had at least one bleed treated with 2 or more doses of N9-GP. While 28.4% of their bleeds were treated with 2 or more doses (hemostatic response: 18, good; 5, moderate), 71.6% were still treated with only 1 dose (hemostatic response: 7, excellent; 49, good; 1, moderate; 1, not reported).

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http://doi.org/10.2147/JBM.S212690

Table 1 OD treatment of bleeds by the number of N9-GP doses

OD treatment arm (N=15)	Number of patients	Number of bleeds
Patients with no bleeds	1	0
All patients with bleeds	14	143
Bleeds treated with only 1 dose	13	120 (83.9%)
Bleeds treated with 2 or more doses	7	23 (16.1%)
Patients with only 1-dose treated bleeds	7	62
Patients with at least one bleed treated with 2 or more doses	7	81
Bleeds treated with only 1 dose		58 (71.6%)
Bleeds treated with 2 or more doses		23 (28.4%)
Patients with recurrent TJ bleeds	2	11
Bleeds treated with only 1 dose		7 (63.6%)
Bleeds treated with 2 or more doses		4 (36.4%)
Patients with other bleeds	5	70
Bleeds treated with only 1 dose		51 (72.9%)
Bleeds treated with 2 or more doses		19 (27.1%)

Abbreviations: N, number of patients; OD, on-demand; TJ, target joint.

Two of the 7 patients experienced 11 recurrent TJ bleeds, 4 (36.4%) of which required treatment with 2 or more doses of N9-GP. One patient, 18 years of age, reported three elbow TJ bleeds in 2 months, which were treated with 1, 5, and 2 doses of N9-GP, respectively. The second patient, 27 years of age, was treated prophylactically with plasma-derived FIX (pdFIX) 100 IU/kg every 3 days prior to entering the OD arm of paradigm 2. He reported two bleeds in 2 weeks in his right ankle TJ; one TJ bleed was treated with 2 doses (1 for early rebleeding) and the second bleed was treated with 6 doses, after which the patient was withdrawn.

The other 5 of the 7 patients experienced 70 bleeds; 72.9% were treated with 1 dose (hemostatic response: 2, excellent; 47, good; 1, moderate; 1, not reported) and 27.1% with 2 or more doses (hemostatic response: 17, good; 2, moderate). Four of these five patients had previously received 2 or 3 high FIX doses (60–81 IU/kg) for treating a bleed before entering the study and reported 63 bleeds while on study, which accounted for 44% of all bleeds in the OD treatment arm (Figure 1). The average N9-GP dose in these four patients ranged from 41.7 to 71.1 IU/kg per bleed and FIX utilization was reduced by 56–80% compared with the patient's historical FIX utilization (Figure 1). The fifth patient was treated prestudy with 1 prescribed infusion of 34 IU/kg pdFIX per bleed with unknown effectiveness and had seven bleeds while on study (6 treated with 1 dose of ~40 IU/kg per protocol and 1 with 2 doses; mean 46.8 IU/kg per bleed).

This post hoc analysis from paradigm 2 supports an important potential role for N9-GP in the OD treatment of mild/moderate bleeds. Modeling based upon the Phase 1 pharmacokinetic study to achieve recommended FIX levels suggested by the World Federation of Hemophilia[1,5] indicated that N9-GP could potentially reduce the number of doses and total FIX utilization compared with recombinant FIX (rFIX) or pdFIX: 1 vs 2 doses for mild/moderate bleeds (40 vs 95–110 IU/kg), 1 vs 6 doses for severe bleeds (80 vs 310–350 IU/kg), and 5 vs 28 doses for intracranial hemorrhage (240 vs 1450–1490 IU/kg).[6]

The recent Bridging Hemophilia Experiences Results and Opportunities into Solutions (B-HERO-S) study in patients with mild-moderate-severe hemophilia in the USA reported that increasing education about self-infusion may be of benefit to individuals, particularly those with mild/moderate hemophilia: treatment is typically given at a hemophilia clinic or hospital and/or patients need assistance from family members or health care professionals; fewer than 10% of patients reported that all their infusions were at home.[7] Delays in recognizing bleeds or receiving help with infusions may also impact outcomes over time. Specifically, B-HERO-S showed that pain, functional impairment, and anxiety/depression were present at higher-than-expected levels in patients with mild/moderate hemophilia B, including affected women, suggesting unmet needs in the management of this population and perhaps undertreatment of bleeding episodes.[8] Coupled with improved education to increase the recognition of bleeds, the ability to treat most bleeds with 1 dose with sustained FIX activity, within the World Federation of Hemophilia guidelines[5] recommendations over many days, offers a potential pathway to improved outcomes.

In conclusion, a single 40 IU/kg dose of N9-GP was effective as an OD treatment for most bleeds in patients with hemophilia B investigated in paradigm 2. For patients who required

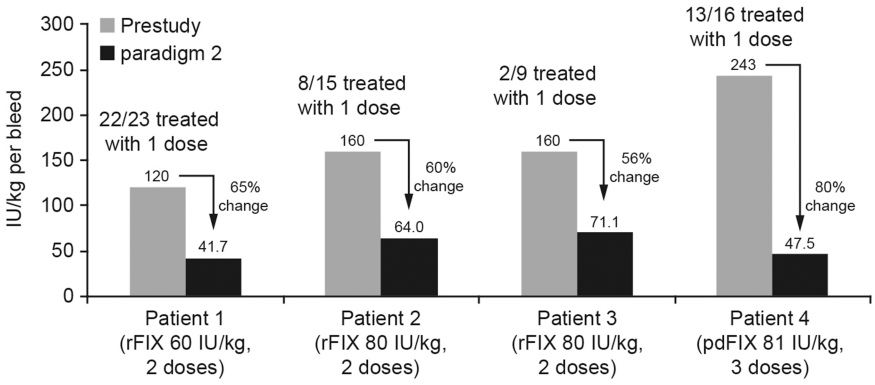

Figure 1 Treatment of patients with a history of requiring multiple high-dose FIX.
Abbreviations: FIX, factor IX; pdFIX, plasma-derived factor IX; rFIX, recombinant factor IX.

additional N9-GP doses, the majority had either recurrent TJ bleeds or a history of multiple high-dose treatment. A prolonged duration of treatment after bleeding and potential change to routine prophylaxis is typical for patients with recurrent TJ bleeds. For patients who may not have required additional dosing of rFIX/pdFIX based upon their phenotype or individual pharmacokinetics, the paradigm 2 analysis supports the predictive modeling that a change to N9-GP would likely be associated with fewer infusions and FIX utilization than rFIX/pdFIX.

Data sharing statement

Novo Nordisk's policy on data sharing may be found at https://www.novonordisk-trials.com/how-access-clinical-trial-datasets.

Acknowledgments

The paradigm 2 trial was sponsored by Novo Nordisk A/S (Bagsværd, Denmark) and is registered with ClinicalTrials.gov (NCT01333111). The sponsor was responsible for trial operations, including data analysis. The authors acknowledge the medical writing assistance of Vathsala Jayanth (Parexel), which was funded by Novo Nordisk A/S.

Author contributions

MAE, CEW, and GY were principal investigators and enrolled and cared for patients during the trial. All authors designed the trial protocol, directed the data analysis, and wrote the manuscript. All authors had access to the primary clinical trial data. All authors were involved in interpretation of the trial results and preparation of the manuscript outline, provided input during the review stages, and approved the final manuscript. The authors assume full responsibility for the accuracy and completeness of the reported data, and agree to be accountable for all aspects of the work.

Disclosure

MAE reports research funding from Pfizer and consulting fees from CSL Behring, Genentech, Roche, Hemabiologics, Novo Nordisk, Pfizer, and Shire. MAE participated in advisory boards, consultation, and educational talks and received personal fees from Sanofi, Novo Nordisk, Takeda and CSL Behring. DLC is an employee of Novo Nordisk Inc. GY reports honoraria and consultancy fees from Alnylam, Bioverativ, CSL Behring, Genentech/Roche, Grifols, Kedrion, Novo Nordisk, and Shire. He also reports personal fees from Bioverativ/Sanofi, CSL Behring, Genentech/Roche, Grifols, Kedrion, Novo Nordisk, Spark, Takeda, and UniQure, during the conduct of the study. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 List of independent ethics committees or institutional review boards that approved the paradigm 2 trial (NCT01333111)

Country	Independent ethics committee/institutional review board
Germany	Ethikkommission Medizinsche Hochschule Hannover Carl-Neuberg-Straße 1 30625 Hannover
France	Comité de Protection des Personnes - Sud Est III Hôpital Edouard Herriot 5 Place d'Arsonval 69003 LYON
Italy	Segreteria Comitato Etico Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Via F.Sforza, 28 20122 Milano
	Comitato Etico per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliero-Universitaria-Careggi Via Pieraccini, 17 50139 Firenze
Japan	IRB of Nara Medical University Hospital 840 Shijo-cho, Kashihara-shi, Nara, 634-8522
	IRB of Nagoya University Hospital 65 Tsurumai-cho, Showa-ku, Nagoya-shi, Aichi, 466-8560
	IRB of Hyogo College of Medicine Hospital 1-1 Mukogawa-Cho, Nishinomiya-shi, Hyogo, 663-8501
	IRB of Ogikubo Hospital 3-1-24,Imagawa, Suginamiku, Tokyo, 167-0035
	IRB of Tokyo Medical University Hospital 6-7-1 Nishishinjuku, Shinjukuku, Tokyo, 160-0023
	IRB of St. Marianna University School of Medicine Hospital 2-16-1 Sugao Miyamae-ku, Kawasaki-shi, Kanagawa, 216-8511
Macedonia	Ethic Committee for investigations in people 50 divizija Skopje Macedonia
Malaysia	Medical Research & Ethics Committee, National Institute of Health D/A Institute Pengurusan Kesihatan Jalan Rumah Sakit, Bangsar 59000 Kuala Lumpur
Netherlands	UMCU Heidelberglaan 100 3584 CX Utrecht

(*Continued*)

Table S1 (Continued).

Country	Independent ethics committee/institutional review board
Russia	Ethic Committee at Ministry of Health and Social Development of Russian Federation 3, Rahmanovsky pereulok Moscow, 127994
Thailand	Committee on Human Right Related to Research Involving Human Subjects Faculty of Medicine, Ramathibodi Hospital Mahidol University 270 Rama VI Road, Ratchathewi, Bangkok 10400
Turkey	Erciyes University Clinical Trials Ethics Committee Erciyes University Deanship of Medical Faculty Melikgazi/KAYSERI
United Kingdom	Berkshire REC South West REC Centre South West REC Centre Level 3 Block B Whitefriars Lewins Mead Bristol, BS1 2NT
	Oxford Radcliffe Hospitals NHS Trust Research & Development Department Manor House The John Radcliffe Hospital Headington Oxford, OX3 9DZ
	The Joint Clinical Trials Office 16th Floor Tower Wing, Guy's Hospital, Great Maze Pond, SE1 9RT
	Royal Free Hampstead NHS Trust Research & Development Royal Free Hospital Pond Street London, NW3 2QG
	Cardiff and Vale University Local Health Board Health Board Second Floor, Tower Block Two, Room 3 University Hospital of Wales Heath Park Cardiff, CF14 4XN
	Hampshire Hospitals NHS Foundation Trust Research & Development, Rm 32, F Floor Aldermaston Road Basingstoke, RG24 9NA

(*Continued*)

Table S1 (Continued).

Country	Independent ethics committee/institutional review board
United States	Western Institutional Review Board 3535 7th Avenue SW Olympia, WA 98502-5010
	Johns Hopkins University 1620 McElderry Street Reed Hall, Suite B-130 Baltimore, MD 2105
	Mount Sinai Hospital Program for Protection of Human Subjects One Gustave L. Levy Place, Box 1075 New York, NY 10029
	The Pennsylvania State University College of Medicine Human Subjects Protection Office Penn State College of Medicine 600 Centerview Drive, Mail Code A115 Hershey, PA 17033
	Children's Hospitals and Clinics of Minnesota 280 North Smith Avenue Suite 4-200 Minneapolis, MN 55102
	Texas Children's Hospital One Baylor Plaza, 600D Houston, TX 77030
	University of Nebraska Medical Center Joint Pediatric Institutional Review Board 987830 Nebraska Medical Center Omaha, NE 68198-7830
	Chesapeake Research Review Inc 7063 Columbia Gateway Drive Suite 110 Columbia, MD 21046
	Children's Hospital Los Angeles Committee on Clinical Investigations Human Subjects Protection Program 4551 Sunset Blvd., MS 23 Los Angeles, CA 90027
	Nemours Children's Clinic Nemours Florida Institutional Review Board 807 Children's Way Jacksonville, FL 32207
	St. Michael's Medical Center IRB 111 Central Avenue Newark, NJ 07102
	The Gulf States Hemophilia & Thrombophilia Center Committee for the Protection of Human Subjects 6410 Fannin Street, Suite 1100
	SUNY Upstate Medical University IRB for the Protection of Human Subjects 750 East Adams Street 1109 WSK Hall Syracuse, NY 13210

(*Continued*)

Table S1 (Continued).

Country	Independent ethics committee/institutional review board
Zambia	Wits Health Consortium (Pty) Ltd 8 Blackwood Avenue Parktown, Gauteng 2193 South Africa