Longitudinal Efficacy and Safety of N9-GP for Prophylaxis and Bleed Control in US Patients

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BACKGROUND & AIMS

- N9-GP (Rebinyn®) is an extended half-life recombinant factor IX (FIX) product with a 40-kDa polyethylene glycol molecule approved for prophylaxis at a dose of 40 IU/kg in adults and children with hemophilia B in the US[1]
- The paradigm trials comprises 7 multinational studies evaluating routine prophylaxis and bleed control with N9-GP in patients with hemophilia
  - Safety, efficacy, and pharmacokinetics of N9-GP were evaluated in previously treated adults/adolescents (paradigm2) and previously treated children (paradigm5) with hemophilia B
  - Long-term safety and efficacy of N9-GP were evaluated in paradigm4, an extension of the paradigm2 trial, and the extension phase of paradigm5
- The objective of the present analysis was to compare the efficacy and safety of N9-GP in US vs global (including US) patients on prophylactic or on-demand therapy

MATERIALS & METHODS

paradigm2

- Male adults/adolescents (aged ≥13 years) with hemophilia B (FIX ≤2%) were treated with N9-GP on-demand for 28 weeks (40 IU/kg for mild/moderate bleeds; 80 IU/kg for severe bleeds) or prophylactically for 52 weeks (10 IU/kg or 40 IU/kg once-weekly [QW] treatment groups)

paradigm4

- paradigm4 was an extension trial of paradigm2 in which patients could change treatment arms

paradigm5

- In paradigm5, children (aged ≤12 years; FIX ≤2%) were administered QW prophylaxis (N9-GP 40 IU/kg) through a 52-week main phase followed by an extension phase for up to 10 years
- Mild/moderate bleeds were treated with 40 IU/kg, while severe bleeds were treated with 80 IU/kg
- Prophylaxis, bleed treatments, and hemostatic effect were captured in electronic diaries

RESULTS

- In total, 59 patients in paradigm2, 67 patients in paradigm4, and 25 patients in paradigm5 received prophylactic N9-GP **(Table 1)**

Table 1 paradigm2, paradigm4, and paradigm5 patient characteristics

	paradigm2						paradigm4[a]						paradigm5	
	Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 40 IU/kg QW	
	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US
Number of patients	30	5	29	6	15	10	21	3	52	16	5	2	25	9
Age at baseline, mean (SD), years	32.4 (13.9)	25.8 (11.9)	30.0 (15.8)	23.5 (15.5)	32.4 (12.0)	30.4 (12.5)	34.6 (14.8)	27.0 (9.6)	31.1 (14.2)	27.7 (13.5)	37.6 (15.4)	35.5 (23.3)	6.5 (3.7)	7.1 (3.7)
Ethnicity, n (%)														
Hispanic or Latino	2 (6.7)	2 (40.0)	-	-	-	-	-	-	2 (3.8)	2 (12.5)	-	-	2 (8.0)	2 (22.2)
Not Hispanic or Latino	28 (93.3)	3 (60.0)	29 (100.0)	6 (100.0)	15 (100.0)	10 (100.0)	21 (100.0)	3 (100.0)	50 (96.2)	14 (87.5)	5 (100.0)	2 (100.0)	23 (92.0)	7 (77.8)
Race, n (%)														
Asian	8 (26.7)	-	5 (17.2)	-	3 (20.0)	-	4 (19.0)	-	9 (17.3)	-	2 (40.0)	-	8 (32.0)	-
Black	2 (6.7)	1 (20.0)	3 (10.3)	1 (16.7)	-	-	1 (4.8)	-	4 (7.7)	2 (12.5)	-	-	1 (4.0)	-
White	16 (53.3)	1 (20.0)	21 (72.4)	5 (83.3)	11 (73.3)	10 (100.0)	16 (76.2)	3 (100.0)	37 (71.2)	12 (75.0)	2 (40.0)	2 (100.0)	13 (52.0)	8 (88.9)
Other	4 (13.3)	3 (60.0)	-	-	1 (6.7)	-	-	-	2 (3.8)	2 (12.5)	1 (20.0)	-	3 (12.0)	1 (11.1)

QW=once weekly.
[a]Patients in paradigm4 who switched treatment arms are represented in multiple columns; patient numbers are based on the treatment arms at the time of each bleed.

Efficacy

- In paradigm2, there were 202 bleeds in 41 patients receiving prophylaxis **(Table 2)**; of these, 1 bleed was severe. Thirty-two of these bleeds occurred in 8 US patients
  - In patients receiving N9-GP 10 IU/kg QW, the median spontaneous annualized bleeding rate (ABR) was 0.97 for global patients and 0.98 for US patients (**Figure 1**)
  - The median spontaneous ABR was 0.00 for global and US patients receiving N9-GP 40 IU/kg QW
  - Fewer bleeds in target joints were observed in patients receiving N9-GP 40 IU/kg QW compared with patients receiving 10 IU/kg QW or on-demand treatment
- In paradigm4, there were 133 bleeds in 43 patients receiving prophylaxis; 51 of these occurred in 13 US patients
  - The median spontaneous ABR was 1.05 for global patients and 0.00 for US patients receiving N9-GP 10 IU/kg QW
  - The median spontaneous ABR was 0.00 for global and US patients receiving N9-GP 40 IU/kg QW
- In paradigm5, there were 128 bleeds in 20 patients; 55 of these occurred in 8 US patients
  - The median spontaneous ABR was 0.00 for global and US patients
  - Treatment success rates for US patients were comparable to those for global patients across trials

Table 2 Median ABRs, target joint bleeds and bleed treatment in paradigm2, paradigm4, and paradigm5

	paradigm2						paradigm4[a]						paradigm5	
	Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 40 IU/kg QW	
	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US
Total number of patients	30	5	29	6	15	10	21	3	52	16	5	2	25	9
Number of patients with bleeds during the treatment period, n	25	5	16	3	14	10	14	2	31	11	5	2	20	8
Mean treatment period, years	0.97	0.92	0.96	1.01	0.51	0.55	0.95	1.32	0.97	1.01	1.13	0.92	6.03	4.36
Bleeds, n	132	23	70	9	143	112	35	4	98	47	73	24	128	55
Median ABR	2.93	3.71	1.04	0.98	15.58	16.40	1.36	1.14	1.00	1.99	12.83	12.89	0.50	1.34
Target joint bleeds, n	49	7	19	2	70	56	3	-	28	9	23	12	3	-
Spontaneous	36	4	16	-	54	41	3	-	14	1	23	12	-	-
Traumatic	13	3	3	2	16	15	-	-	14	8	-	-	3	-
Bleed treatment success rate, %	86.9	87.0	97.1	100.0	95.1	97.3	97.1	100.0	94.8	91.3	93.2	87.5	89.1	89.1

ABRs=annualized bleeding rates; QW=once weekly.
[a]Patients in paradigm4 who switched treatment arms are represented in multiple columns; patient numbers are based on the treatment arms at the time of each bleed.

CONCLUSIONS

- N9-GP was effective during the main and extension trials in both global and US patients with hemophilia B
- In addition, N9-GP was well tolerated, and no safety issues were identified throughout the paradigm program

Safety

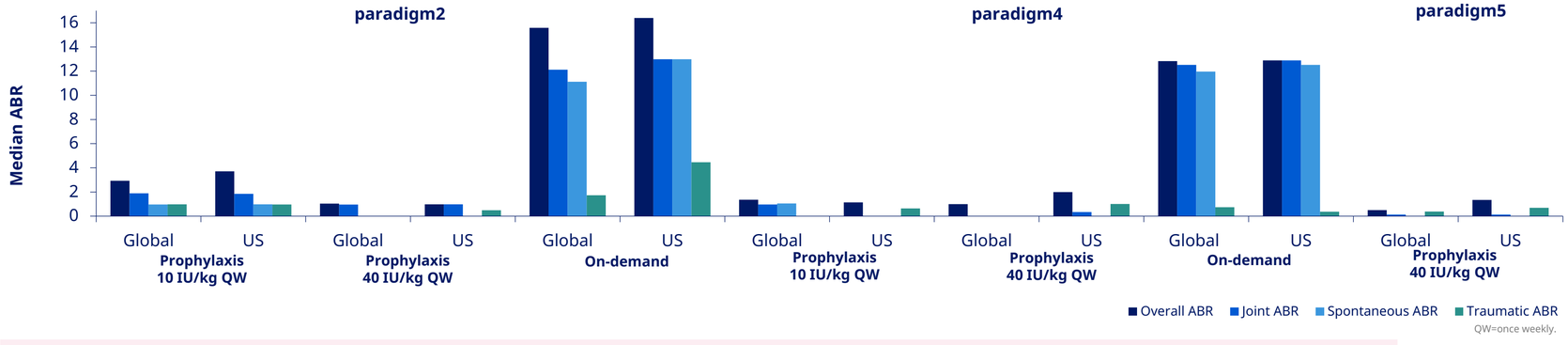
- Across the 3 studies
  - ≥96% of adverse events (AEs; **Table 3**) were of mild to moderate severity
  - Zero factor IX inhibitors were reported
  - There were 0 confirmed thromboembolic events
  - No serious AEs (SAEs) were judged to be treatment related
- There were 16 treatment-related AEs in patients on the prophylactic regimen in paradigm2, 3 of which occurred in US patients
- There were 4 treatment-related AEs in patients on the prophylactic regimen in paradigm4, none of which occurred in US patients
- There were 8 treatment-related AEs in paradigm5, 6 of which were in US patients
- AEs included injection site reactions, nausea, and headache

Table 3 Overall safety data from paradigm2, paradigm4, and paradigm5

	paradigm2						paradigm4[a]						paradigm5	
	Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 10 IU/kg QW		Prophylaxis 40 IU/kg QW		On-demand		Prophylaxis 40 IU/kg QW	
	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US	Global	US
Number of patients with AEs	24	4	25	6	11	7	15	1	32	9	5	2	24	8
Total time in trial, years	28.97	4.6	27.91	6.05	7.73	5.52	19.09	3.95	48.44	15.41	5.65	1.84	150.87	39.24
Total AEs	76	11	107	36	32	19	46	1	91	40	18	10	621	275
Serious AEs	1	-	3	-	-	-	1	-	5	2	-	-	7	1
Treatment-related AEs	8	-	8	3	3	2	-	-	4	-	-	-	8	6
Treatment-related SAEs	-	-	-	-	-	-	-	-	-	-	-	-	-	-

AEs=adverse events; QW=once weekly; SAEs=serious adverse events.
[a]Patients in paradigm4 who switched treatment arms are represented in multiple columns; patient numbers are based on the treatment arms at the time of each bleed.

Figure 1 Median overall ABR, joint ABR, spontaneous ABR, and traumatic ABR for global and US patients in paradigm2, paradigm4, and paradigm5



QW=once weekly.

REFERENCE

1. Rebinyn [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2022.

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