Comparison of the relationship between factor IX activity and bleeding risk during prophylaxis with nonacog beta pegol (N9-GP)

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Objective

- To evaluate the impact of the factor IX (FIX) activity profile on bleeding risk in patients receiving once-weekly N9-GP prophylaxis, taking N9-GP dose level and time since last dose into consideration.

Conclusions

- Patients achieved greater prophylactic protection with 40 IU/kg N9-GP once-weekly dosing than 10 IU/kg.
- Achieving close to physiological FIX activity levels for extended periods could potentially be important in delaying the progression of underlying joint disease for patients with haemophilia B.

Introduction

- Nonacog beta pegol (N9-GP) is a recombinant factor IX (rFIX) molecule that has been glycoPEGylated to achieve an extended half-life.[1]
- N9-GP was developed to prevent and treat bleeds in haemophilia B with less frequent dosing, and to achieve higher FIX activity levels compared with non-modified FIX products.
- In a pivotal phase 3 trial, paradigm™2, N9-GP was well tolerated and provided effective once-weekly prophylaxis and bleed control in previously treated adult and adolescent patients with haemophilia B.[2]
- Here, we review findings from a post-hoc evaluation of the impact of FIX activity profile on bleeding risk in patients from paradigm™2, taking N9-GP dose level and time since last dose into consideration.

Methods

Patients

- Male patients aged 13–70 years with haemophilia B (FIX activity ≤2%), with no history of FIX inhibitors and with ≥150 exposure days to any FIX product were included in paradigm™2.

Trial design

- The trial was a multicentre, single-blind, non-controlled phase 3 trial, in which patients were randomised 1:1 to receive 10 or 40 IU/kg once-weekly N9-GP prophylaxis for 52 weeks.
- The dose of 10 IU/kg functioned as an active control arm mimicking therapy with conventional non-modified FIX products.

Analyses

- The current post-hoc analysis compared annualised bleeding rates (ABR) for each arm.
- FIX activity was assessed at steady state in a subset of patients (n=59).
- Bleeding risk by time since last dose was analysed using Cox regression, including regimen and shared frailty to account for within-patient correlation.

Results

ABR

- Estimated ABR for patients treated with 40 IU/kg N9-GP was 49% lower versus for those who received 10 IU/kg (p=0.033, Table 1).
- On-study ABRs were lower than historical bleeding rates regardless of pre-trial treatment regimen; for patients who received on-demand treatment prior to the trial there was a marked decrease in both the 10 IU/kg and 40 IU/kg arms (Figure 1).

Risk of bleeding

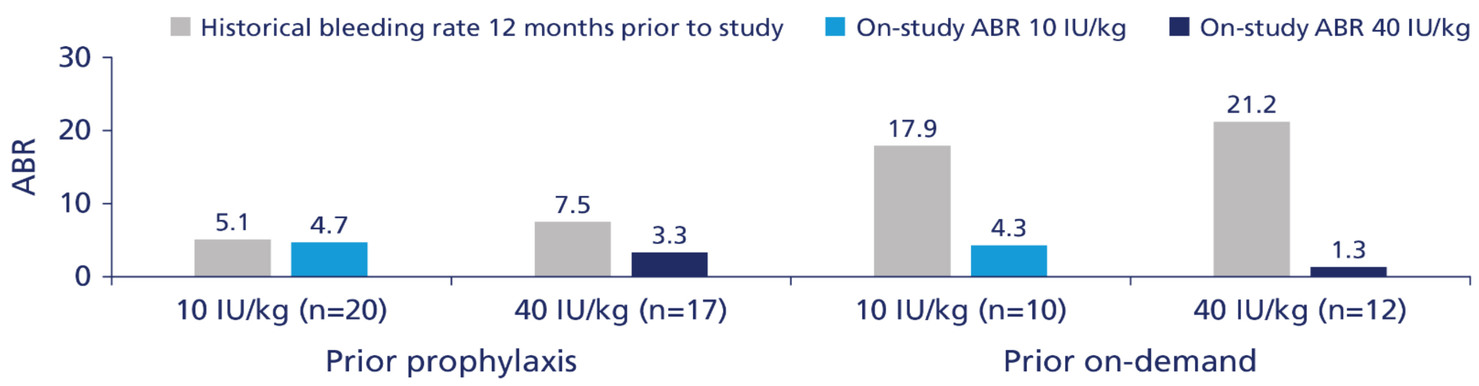
- For all bleeds, the bleeding risk by time since last dose was 1.93 times higher in the 10 IU/kg arm versus the 40 IU/kg arm (p=0.0123), and 2.72 times higher for spontaneous bleeds (p=0.0143, Table 2).

Table 1 ABR by prophylaxis dose.

	Prophylaxis		
	10 IU/kg	40 IU/kg	Both
Number of patients	30	29	59
Number of patients with bleeds, n (%)	25 (83.3)	16 (55.2)	41 (69.5)
Number of bleeds	132	70	202
Bleeds per patient (min; max)	0.0; 17.0	0.0; 17.0	0.0; 17.0
Mean treatment period (years)	0.97	0.96	0.96
Individual ABRs			
N	30	29	59
Median	2.93	1.04	2.04
Interquartile range	0.99; 6.02	0.00; 4.00	0.00; 5.00
Poisson estimate of ABR[a]	4.56	2.51	3.55
95% CI	3.01; 6.90	1.42; 4.43	2.53; 4.98
p-value	0.402	0.013	0.040
Estimated ABR reduction (adjusted)[b]			
40 IU/kg versus 10 IU/kg	–	–	0.49
95% CI	–	–	0.05; 0.73
p-value[c]	–	–	0.033

ABR, annualised bleeding rate; CI, confidence interval.
[a]Based on a Poisson regression model with dose as a factor allowing for over-dispersion and using treatment duration as an offset. p-values are from the one-sided test of the null hypothesis that the ABR is at least 4.8 evaluated at the 2.5% level. [b]Reduction: 1–ABR relative risk. Adjusted estimates are based on a model with covariate adjustment for prior treatment and historical ABR. The adjusted estimates exclude two patients receiving 10 IU/kg who are missing their historical ABR. Positive values indicate a decrease in bleeding rate and negative values indicate an increase. [c]A two-sided test of the null hypothesis that there is no difference between the two doses evaluated at the 5% level.

Figure 1 Historical versus on-study ABR by pre-trial treatment regimen.



ABR, annualised bleeding rate.

Table 2 Hazard ratio of bleeds by time since last N9-GP dose – for all dosing intervals.

	Prophylaxis 10 IU/kg versus 40 IU/kg
All bleeds	
Hazard ratio	1.93
p-value	0.0123
Spontaneous bleeds	
Hazard ratio	2.72
p-value	0.0143
Traumatic bleeds	
Hazard ratio	1.15
p-value	0.4205

The cumulative hazard of bleed versus time since last administered dose was estimated in a Cox-proportional hazard model with treatment included as a fixed effect and patient modelled as a shared frailty. In this shared frailty model, the within-patient correlation is taken into account by assuming patient frailty follows a log-normal distribution.

FIX activity

- Peak FIX activity range at steady-state:
  - [0.23; 0.55] IU/ml for 10 IU/kg
  - [0.72; 1.44] IU/ml for 40 IU/kg.
- Trough FIX activity range at steady-state:
  - [0.06; 0.20] IU/ml for 10 IU/kg
  - [0.25; 0.43] IU/ml for 40 IU/kg.
- Lower bleeding risk appears to be associated with higher FIX activity, in favour of 40 IU/kg.

References

1. Negrier C, *et al*. *Blood* 2011;118:2695–2701.
2. Collins PW, *et al*. *Blood* 2014;124:3880–3886.

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http://preview.parexel-mms.com/ISTH-2017/N9-GP-Young.aspx